NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Fedratinib for treating disease-related splenomegaly or symptoms in myelofibrosis (Review of TA756) [ID5115]

Committee Papers

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Fedratinib for treating disease-related splenomegaly or symptoms in myelofibrosis (Review of TA756) [ID5115]

Contents:

The following documents are made available to stakeholders:

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

1. **Company submission** from Celgene UK – a BMS company:
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. MPN Voice-Leukaemia Care
   b. National Disease Registration Service SACT report

4. **Expert personal perspectives** from:
   a. Professor Tim Somervaille – clinical expert, nominated by Celgene UK – a BMS company
   b. Andy Tattersall – patient expert, nominated by MPN Voice
   c. Jonathan Mathias – patient expert, nominated by MPN Voice

5. **External Assessment Report** prepared by School of Health and Related Research, University of Sheffield

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

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

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Fedratinib for treating disease-related splenomegaly or symptoms in myelofibrosis (CDF review of TA756) [ID5115]

Document B

Company evidence submission

March 2024

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CONTENTS

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TABLES

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FIGURES

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

Fedratinib (INREBIC®) in the treatment of disease-related splenomegaly or symptoms in myelofibrosis was evaluated by the National Institute for Health and Care Excellence (NICE) in December 2021 (TA756). During the evaluation, a number of uncertainties regarding the efficacy of fedratinib were outlined. The committee believed that fedratinib is clinically effective, but the lack of comparator data made assessing the comparative effectiveness challenging. Furthermore, the indirect treatment comparison suggested fedratinib improved response compared with best available therapy (BAT), but there were uncertainties due to the methodological approach. The committee also identified the ability of fedratinib to extend overall survival (OS) compared with BAT as a key uncertainty. After the evaluation, fedratinib was recommended for use within the Cancer Drugs Fund (CDF) to allow a period of managed access, supported by additional data collection to answer the clinical uncertainty.

During the CDF managed access stage, further evidence on fedratinib in the post-ruxolitinib setting was collected through the FREEDOM-2 trial to address these uncertainties. FREEDOM-2 is a multicentre, open-label, randomised phase 3 study to evaluate the efficacy and safety of fedratinib compared with BAT in participants with Dynamic International Prognostic Scoring System (DIPSS)–intermediate or high-risk primary myelofibrosis (PMF), post-polycythaemia vera myelofibrosis (post-PV MF), or post-essential thrombocythemia myelofibrosis (post-ET MF), and previously treated with ruxolitinib. In addition, supplementary data showing the real-world effectiveness of fedratinib in the CDF population has been routinely collected from Systemic Anti-Cancer Therapy (SACT) data set and has been analysed and reported here.

B.1.1 Decision problem

The marketing authorisation for fedratinib (INREBIC®) is for “the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis who are Janus kinase (JAK) inhibitor naive or who have been treated with ruxolitinib.” This submission focuses only on those patients who have been exposed to ruxolitinib. The proposed position in the treatment pathway is narrower than the marketing authorisation because this position reflects the unmet need within the myelofibrosis treatment pathway and reflects where clinicians anticipate using fedratinib in UK practice due to the current lack of active treatments available and in line with subsequent CDF access.

The decision problem addressed is summarised in Table 1.

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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, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis who have been treated with ruxolitinib.	This position is narrower than the marketing authorisation for fedratinib because the population of patients previously treated with ruxolitinib reflects where fedratinib provides the most clinical benefit and cost-effectiveness. This approach was accepted by NICE as appropriate during the original submission.
Intervention	Fedratinib 400 mg	Fedratinib 400 mg	Not applicable
Comparator(s)	For people whose disease was previously treated with ruxolitinib or if ruxolitinib is not appropriate (including people with low or intermediate-1 risk disease): ▪ Established clinical practice (including but not limited to hydroxycarbamide, other chemotherapies, androgens, splenectomy, radiation therapy, erythropoietin, and RBC transfusion) ▪ Momelotinib (subject to NICE evaluation)	Previous treatment with ruxolitinib or if ruxolitinib is not appropriate (including people with low or intermediate-1 risk disease). Established clinical practice, otherwise referred to as *BAT* (including but not limited to ruxolitinib, hydroxycarbamide, other chemotherapies, androgens, splenectomy, radiation therapy, erythropoietin, and RBC transfusion)	This appraisal focuses on standard of care available in the UK (ruxolitinib or BAT). Momelotinib is currently subject to a NICE appraisal and is not currently established in NHS clinical practice (in England and Wales) and therefore cannot be viewed as a comparator in the evaluation of fedratinib.
Outcomes	The outcome measures to be considered include: ▪ Spleen size ▪ Symptom relief (including itch, pain and fatigue) ▪ OS ▪ Leukaemia-free survival ▪ Response rate ▪ Haematological parameters (including RBC transfusion and blood count) ▪ Adverse effects of treatment ▪ HRQOL	The outcome measures to be considered include: ▪ Primary outcome – Percentage of patients with ≥ 35% SVR in the fedratinib and BAT arms ▪ Key secondary outcomes – Percentage of patients with at least 50% reduction in myelofibrosis-associated symptoms – Percentage of patients with ≥ 25% SVR ▪ Secondary outcomes – Spleen response rate	Neither FREEDOM-2 nor the SACT data reported leukaemia-free survival. FREEDOM-2 reported spleen and disease progression-free survival, which was defined as time from randomisation to death due to any reason or disease progression (modified IWG-MRT 2013 including ≥ 25% increase in spleen volume by MRI/CT scan). Therefore, leukaemia-free survival will not be reported.

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
		– Durability of response – Spleen and disease progression-free survival – OS – Adverse effects of treatment – HRQOL ▪ Exploratory outcomes – Haematological parameters (including RBC transfusion and blood count) – Time to spleen response – Best spleen volume response rate	
Subgroups to be considered	▪ People whose disease was previously treated with a JAK inhibitor ▪ Prognostic factors such as haemoglobin < 10 g/dL, leukocyte count > 25 × 10^9/L, circulating blasts (immature blood cells) ≥ 1%, presence of constitutional symptoms, or platelet counts	No subgroup analyses are planned.	BMS are presenting the most relevant case. FREEDOM-2 was designed to align with the population of interest for this assessment. Myeloblasts ≥ 5% in peripheral blood was an exclusion criterion for FREEDOM-2.

BAT = best available therapy; CT = computed tomography; HRQOL = health-related quality of life; IWG-MRT = International Working Group-Myeloproliferative Neoplasms Research and Treatment; JAK = Janus kinase; MRI = magnetic resonance imaging; NHS = National Health Service; OS = overall survival; RBC = red blood cell; SACT = Systemic Anti-Cancer Therapy; SVR = spleen volume reduction; UK = United Kingdom.

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B.1.2 Description of the technology being evaluated

A summary description of fedratinib, including details of its mechanism of action and marketing authorisation, is provided in Table 2.

Appendix C provides a draft summary of the product characteristics (SmPC).

Table 2. Technology being evaluated

UK approved name and brand name	Fedratinib (INREBIC®)
Mechanism of action	Fedratinib is an oral kinase inhibitor with activity against wild-type and mutationally activated JAK2. Fedratinib selectively inhibits JAK2, with higher inhibitory activity for JAK2 over family members JAK1, JAK3, and TYK2. Fedratinib is a more selective inhibitor of JAK2 than ruxolitinib, which inhibits both subtypes JAK1 and JAK2. Abnormal activation of JAK2 is associated with myeloproliferative neoplasms, including primary myelofibrosis, essential thrombocythaemia, and polycythaemia vera. In cell models expressing mutationally active JAK2, fedratinib reduced phosphorylation of STAT proteins, inhibited cell proliferation, and induced apoptotic cell death. In mouse models of JAK2-driven myeloproliferative disease, fedratinib blocked phosphorylation of STAT 3/5 and improved survival, white blood cell counts, haematocrit, splenomegaly, and bone marrow fibrosis.
Marketing authorisation/CE mark status	A marketing authorisation application for the indication below was submitted to the EMA in December 2019. The date of CHMP positive opinion was December 2020, and the date of regulatory approval was February 2021.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The indication for fedratinib is: "for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis who are JAK inhibitor naive or who have been treated with ruxolitinib." Fedratinib has not been studied in people with platelets < 50 × 10^9/L at baseline and may not be appropriate for use in this population.
Method of administration and dosage	Fedratinib is administered orally as a single daily dose of 400 mg (four 100 mg tablets) taken with or without food.
Additional tests or investigations	Thiamine levels in individuals should be assessed before starting treatment with fedratinib and during treatment as clinically indicated (e.g., each month for the first 3 months and every 3 months thereafter). Fedratinib treatment should not be started in individuals with thiamine deficiency.
List price and average cost of a course of treatment	£6,119.68
Patient access scheme (if applicable)	[redacted]

CHMP = Committee for Medicinal Products for Human Use; EMA = European Medicines Agency; JAK = Janus kinase; STAT = signal transducer and activator of transcription; TYK2 = tyrosine kinase 2; UK = United Kingdom.

Source: Inrebic SmPC[1]

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B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Overview of the disease

Myelofibrosis is a rare haematological disorder characterised by abnormal cytopenias, bone marrow fibrosis, and extramedullary haematopoiesis; myelofibrosis often results in splenomegaly, constitutional symptoms, and shortened survival.[2-5] Most people with myelofibrosis have a gene variant that results in constitutive activation of the JAK/signal transducer and activator of transcription (STAT) signalling pathway.[6,7] Activation of this pathway results in cell proliferation, inhibition of cell death, and clonal expansion of myeloproliferative malignant cells. The abnormal proliferation of pluripotent haematopoietic stem cells that release inflammatory cytokines and growth factors in the bone marrow leads to marrow fibrosis. Progressive bone marrow fibrosis results in release of the malignant stem cells into the circulation and may result in extramedullary haematopoiesis, manifesting as splenomegaly. Extramedullary haematopoiesis is not able to fully compensate for the loss of production of blood cells in the bone marrow; as a result, individuals experience a decrease in one or more blood cell types, i.e., cytopenias (most commonly anaemia and thrombocytopenia). Myelofibrosis may also undergo transformation to acute myeloid leukaemia (AML).[8]

The disease can present as PMF or secondary to polycythaemia vera or essential thrombocythaemia. Myelofibrosis is diagnosed and stratified by risk using one of the following scoring systems: the International Prognostic Scoring System (IPSS), the DIPSS or DIPSS Plus.[9] These are used to classify individuals into 1 of 4 risk groups (low, intermediate-1, intermediate-2, and high) based on factors such as age, presence of constitutional symptoms, and haematological parameters. Approximately half of people with myelofibrosis are found to have either intermediate-2 or high-risk myelofibrosis,[10] which is associated with a poor overall prognosis and very limited survival time.[11]

B.1.3.2 Epidemiology and prognosis

Myelofibrosis typically occurs more frequently with increasing age, with the median age at diagnosis being approximately 65 years.[12-14] It affects slightly more men (62%) than women (38%).[12] Epidemiological estimates for myelofibrosis in people in the United Kingdom (UK) suggest a 10-year prevalence of 3.2 per 100,000 and an annual incidence of 0.6 per 100,000.[15] This suggests that the total population of people with myelofibrosis is 2,130, half of whom are expected to have intermediate-2 and high-risk disease.

People within these risk groups represent a population with considerably worse outcomes compared with people with intermediate-1 or low risk disease.[8,16,17] Currently, only ruxolitinib is recommended by NICE for use in patients with intermediate-2 or high-risk disease.[10] When patients become relapsed, refractory or intolerant to treatment, survival outcomes are poor with several published reports demonstrating a median OS of 13-16 months post-ruxolitinib treatment.[10,18-20] The poor survival outcomes in these patients are attributable to the lack of effective treatment options in the relapsed, refractory and intolerant to ruxolitinib setting, with many patients on suboptimal treatment (see Section B.1.3.4).[18,19] Data from clinical trials indicate that 45% to 89% of patients who are relapsed and refractory to ruxolitinib continue suboptimal ruxolitinib treatment with limited benefits in the absence of other active treatment options.[21-24]

B.1.3.3 Physical and psychological burden of disease

Over 80% of people with myelofibrosis experience splenomegaly, while other clinical manifestations of myelofibrosis include symptoms associated with cytopenias (> 35% of people), fatigue (> 90%), and

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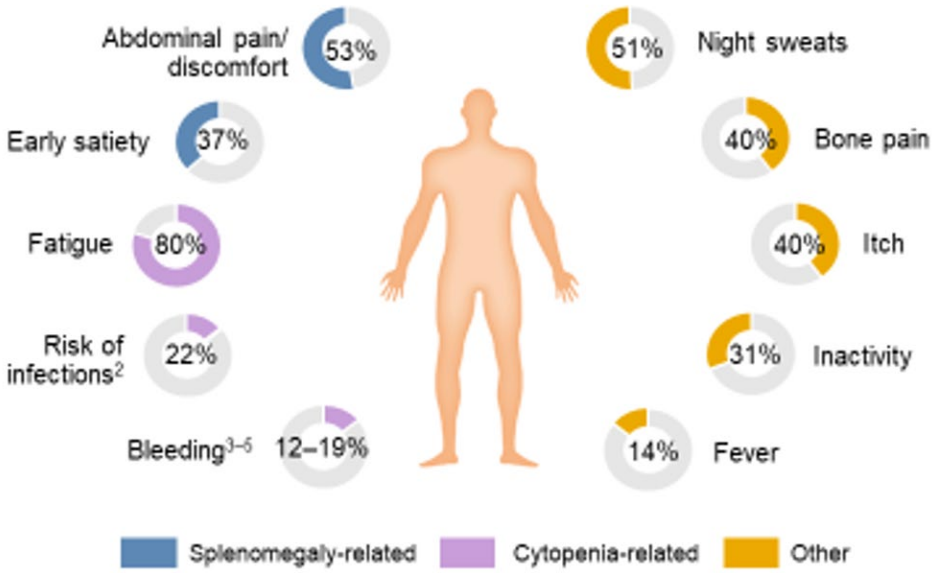
constitutional symptoms (~ 30%).[16] Myelofibrosis is associated with a range of debilitating symptoms that may worsen as the disease progresses and can have a major impact on health-related quality of life (HRQOL).[2,3,25] These stem from the pathological changes in haematopoiesis and the bone marrow, as described above. Splenomegaly can lead to abdominal pain, early satiety, and portal hypertension, whereas progressive bone marrow fibrosis leads to worsening cytopenias, particularly thrombocytopenia and anaemia.[2] Anaemia is associated with fatigue, weakness, palpitations, bone pain, and dyspnoea[2], whereas cytopenias, such as thrombocytopenia and neutropenia, result in complications such as petechiae and infection, respectively. The risk of cytopenias increases with disease progression, resulting in more severe symptoms and an increased risk of leukaemic transformation.

Although extramedullary haematopoiesis predominantly occurs in the spleen and liver, it can also occur in other organs resulting in further complications such as chronic headache, spinal cord compression and pleural effusions.[2]

There are also a range of constitutional symptoms that result from abnormal cytokine production related to the proliferation of progenitor cells. These include fatigue, pruritis, night sweats, fever and cachexia (leading to weight loss) (Figure 1).[2,3,26]

Approximately 10% to 20% of people with PMF will progress to AML.[27] These people have dismal outcomes, with OS ranging from 3 to 8 months and a 1-year survival rate of 5% to 10%.[13]

Figure 1. Debilitating symptoms of myelofibrosis



Adapted from Mesa et al.[26]; Polverelli et al.[28]; Devendra et al.[29]; Kander et al.[30]; Finazzi et al.[31]

Studies reporting on the impact of myelofibrosis symptoms on HRQOL suggest that myelofibrosis particularly impacts physical and social function, and this impact increases with disease progression.[25,26,32] The negative effect on HRQOL experienced by people with myelofibrosis is comparable with that reported for people with recurrent cancer and represents a clinically meaningful reduction in the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Quality of Life of Cancer Patients (Core) (EORTC QLQ-C30) global health score compared with the general population.[25] Many people reduce their working hours or take early retirement because of myelofibrosis.[26,33,34]

In patients who have been treated with ruxolitinib, the physical and psychological burden of myelofibrosis is particularly pronounced. A comparison of the HRQOL at baseline for JAK-naive patients from one of the ruxolitinib pivotal trials, COMFORT-II,[35] with baseline data for ruxolitinib-

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exposed patients included in the fedratinib JAKARTA-2 trial suggests that HRQOL is worse in people who have been treated with ruxolitinib. Both studies assessed HRQOL using the EORTC QLQ-C30. In FREEDOM-2, HRQOL was assessed by EQ-5D-5L in ruxolitinib-experienced patients who were treated with fedratinib. The results showed a clinically meaningful change from cycle 2 day 1 (C2D1) through C5D1, with a mean (standard error of the mean [SEM]) change from baseline of 6.2 (18.97) for patients treated with fedratinib (see Section B.2.6.1.4).[36]

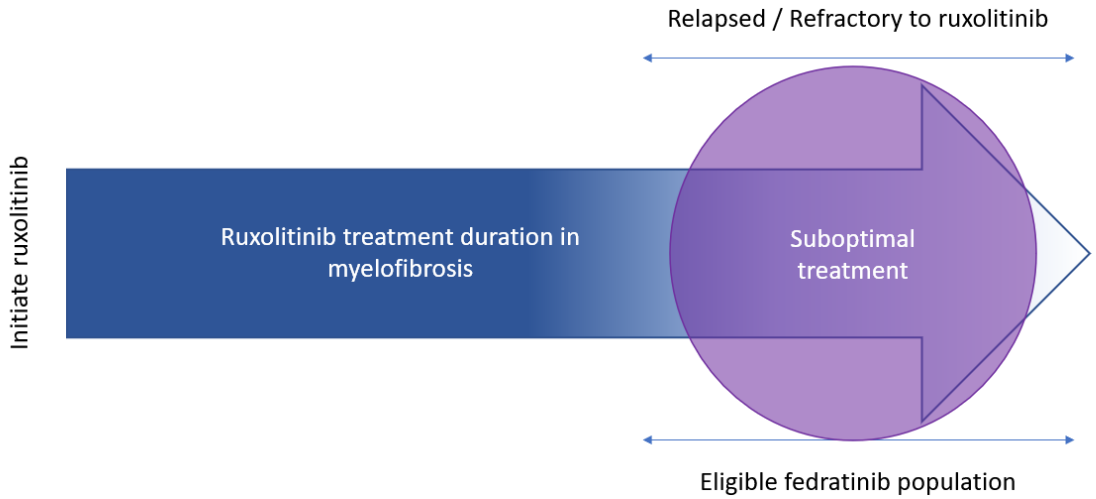
B.1.3.4 Clinical pathway of care

Allogeneic stem cell transplant is the only potentially curative treatment of myelofibrosis; however, it is only suitable for people who are fit enough to undergo treatment as it is associated with considerable morbidity and mortality.[37] Allogeneic stem cell transplant is generally only considered for people with intermediate-2 or high-risk myelofibrosis, of whom only 5% to 10% will meet eligibility criteria for such an intensive therapy.[38,39]

In first-line treatment, options aim to relieve debilitating symptoms, particularly splenomegaly and cytopenia, and improve HRQOL. This includes targeted therapy with JAK inhibitors such as ruxolitinib. Ruxolitinib is the only targeted treatment recommended for use in people with myelofibrosis (with intermediate-2 and high-risk disease) in clinical practice in the UK.[10]

There are considerable limitations associated with treatment with ruxolitinib. Of patients treated with ruxolitinib in clinical trials so far, only 28% to 42% have achieved the primary endpoint of 35% or more spleen volume reduction (SVR) from baseline.[32,40,41] Reports from the COMFORT long-term follow-up trials state more than 50% of patients discontinue ruxolitinib treatment after 3-5 years[24]; however, this may not be reflective of UK clinical practice. Feedback from UK clinicians, including feedback from an advisory board, revealed that many patients continue to receive suboptimal treatment with ruxolitinib, despite being relapsed or refractory (Figure 2). Reasons for this include the lack of treatment options and concerns regarding the potential for a proinflammatory state and acute deterioration of the patient due to ruxolitinib withdrawal.[23,42] These withdrawal symptoms include acute relapse of disease symptoms, accelerated splenomegaly, worsening of cytopenias, and occasional haemodynamic decompensation (including a septic shock-like syndrome).[43]

Figure 2. Current treatment duration in patients who respond to ruxolitinib



BAT = best available therapy.

This continuation of suboptimal ruxolitinib in UK clinical practice aligns with observations from PERSIST-2 and SIMPLIFY-2, where considerable proportions of participants in the BAT arms were receiving ruxolitinib (45% and 89%, respectively).[21-23] BAT includes treatment options that are largely

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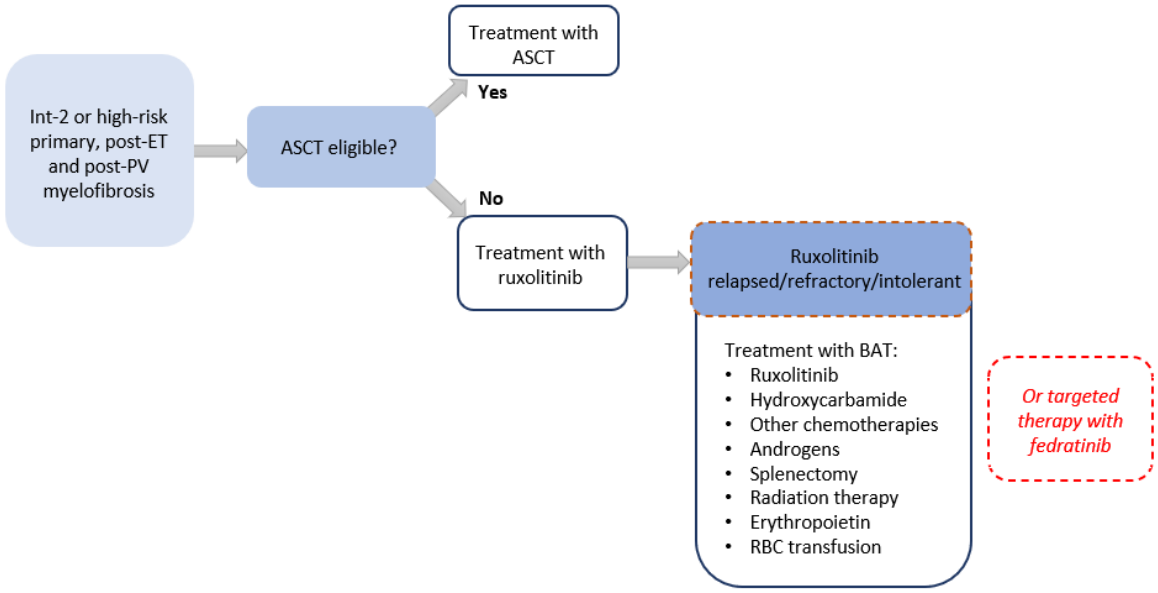
supportive and do not significantly alter the course of the disease. These may also include treatments such as hydroxycarbamide, other chemotherapies, androgens, splenectomy, radiation therapy, erythropoietin, and red blood cell (RBC) transfusion.

Patients relapsed and refractory to ruxolitinib have a reduced life expectancy, with an estimated median OS of 13-16 months after discontinuation.[10,18-20] Data on survival in patients who continue suboptimal ruxolitinib are uncertain; however, it is not expected to be significantly greater than observed in the literature, which is supported by clinical experts.[25]

Given that there are currently no disease-modifying treatment options available in the UK to patients who no longer respond to ruxolitinib, fedratinib was introduced under the CDF. The introduction of fedratinib to the pathway of care provides an opportunity for targeted therapy in a patient population otherwise associated with poor survival outcomes.

Figure 3 presents the clinical pathway of care for people with myelofibrosis in England and the position of fedratinib under the CDF within this pathway.

Figure 3. Clinical pathway of care for people with intermediate-2 and high-risk myelofibrosis in England



ASCT = allogenic stem cell transplant; BAT = best available therapy; ET = essential thrombocythaemia; Int = intermediate; PV = polycythaemia vera; RBC = red blood cell.

B.1.3.5 Unmet medical need

In the current clinical pathway of care, ruxolitinib is the only targeted treatment available and is associated with low response rates, with less than half of participants in clinical trials achieving the primary endpoint.[32,40] In patients who do respond, many will become relapsed or refractory to ruxolitinib over time. In lieu of alternative treatment options, relapsed and refractory patients remain on suboptimal therapy.[23,42] Outcomes in patients no longer responding to ruxolitinib are poor, with a loss of response associated with worse symptoms and an increased spleen size, causing detriments to HRQOL. There is a significant unmet need for a new therapy to address this and provide an alternative treatment option so that clinicians do not have to resort to using limited healthcare resources for suboptimal treatment.

Fedratinib, a targeted and novel therapy, offers an effective treatment option that has shown a clinically meaningful response in patients who have been treated with ruxolitinib. These benefits lead to

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considerable HRQOL improvements and expected improvements in long-term survival in a patient population that would otherwise experience poor outcomes.

B.1.4 Equality considerations

No potential equality considerations have been raised for the use of fedratinib in people with myelofibrosis.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being evaluated.

In summary, a systematic literature review (SLR) was conducted in February 2020 for primary intervention trials (randomised controlled trials and prospective non–randomised controlled trials) assessing the efficacy and safety of fedratinib or comparator therapies in people with myelofibrosis. Since February 2020, no other pharmaceuticals have been approved by NICE for this indication. Therefore, no further evidence is anticipated to be found other than the pivotal trial FREEDOM-2 (providing head-to-head data); thus, an update of the February 2020 SLR would not affect this submission.

The SLR identified 2 key studies that evaluated fedratinib as an active intervention:

- The phase 3 trial, JAKARTA, investigated the safety and efficacy of fedratinib in the ruxolitinib-naive population.
- The phase 2 trial, JAKARTA-2, investigated the safety and efficacy of fedratinib in patients previously treated with ruxolitinib.

Since the SLR was conducted, the following clinical trials have been either completed or have had their preliminary results analysed:

- The phase 3 single-armed trial, FREEDOM, investigated the safety and efficacy of fedratinib in patients previously treated with ruxolitinib (completed).
- The phase 3 trial, FREEDOM-2, investigates the safety and efficacy of fedratinib compared with BAT in patients previously treated with ruxolitinib (the trial is still ongoing but not recruiting).

JAKARTA was a randomised, double-blind, placebo-controlled, phase 3 trial that compared 400 mg or 500 mg fedratinib with placebo in participants with intermediate-2 or high-risk PMF, post-PV MF, or post-ET MF with splenomegaly. Based on the lack of a head-to-head comparator and the study taking place in the ruxolitinib-naive population, the study is not relevant to this submission and is not included in the main dossier. Details and results of this study are presented in Appendix D as supportive evidence.

JAKARTA-2 was a phase 2, multicentre, open-label, single-arm study that evaluated the efficacy of a once daily, 400 mg dose of fedratinib in 97 participants previously treated with ruxolitinib and was included in the original NICE technology appraisal assessment of fedratinib (TA756). JAKARTA-2 has not been used to populate the model for this submission; therefore, details and results of this study are presented in Appendix D as supportive evidence.

FREEDOM was a phase 3, single-arm, US-based, open-label study of 38 participants previously treated with ruxolitinib who had with intermediate-2 or high-risk PMF, post-PV MF, or post-ET MF. This

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study was not included in the economic model because it did not include a head-to-head comparison. A summary of this study is Appendix D as supportive evidence.

B.2.2 List of relevant clinical effectiveness evidence

The key clinical study used for this submission is FREEDOM-2, a phase 3, open-label, randomised study of 201 participants with intermediate-2 or high-risk PMF, post-PV MF, or post-ET MF, comparing fedratinib with BAT (Table 3).

Because FREEDOM-2 provides direct evidence for fedratinib compared with BAT in a patient population that has been treated with ruxolitinib, it forms the key source of clinical and economic evidence in this submission and is described in detail in the following sections.

Furthermore, National Health Service (NHS) England have evaluated the real-world treatment effectiveness of fedratinib in the CDF population during the managed access period. This report presents the results of the use of fedratinib in clinical practice in England, using the routinely collected SACT data set (Table 4).

The SACT data were not used to populate the economic model but has been included as supplementary evidence and summarised in Sections B.2.2-B.2.4 and B.2.6. This study was not included in the economic model because it does not report all the key outcomes, does not have sufficient time for OS follow-up, and does not compare the outcome of fedratinib with BAT.

Table 3. Primary source of clinical effectiveness evidence: FREEDOM-2 (data cut, December 2022)

Study	NCT03952039 (FREEDOM-2)
Study design	A phase 3, multicentre, open-label, randomised, 2-arm study
Population	201 participants previously treated with ruxolitinib and with a current diagnosis of intermediate-2 or high-risk primary myelofibrosis, post-polycythaemia vera myelofibrosis, or post-essential thrombocythaemia myelofibrosis
Intervention(s)	400 mg fedratinib
Comparator(s)	BAT
Indicate if study supports application for marketing authorisation	No
Indicate if study used in the economic model	Yes
Rationale if study not used in model	Not applicable
Reported outcomes specified in the decision problem	▪ Spleen size ▪ Symptom relief ▪ Durability of response ▪ Haematological parameters ▪ Overall survival ▪ Adverse effects of treatment ▪ Health-related quality of life
All other reported outcomes	▪ Duration of response

BAT = best available therapy.

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Table 4. Clinical effectiveness evidence: SACT data cohort study

Study	SACT data cohort study
Study design	Real-world data collection to support the NICE reappraisal of fedratinib
Population	66 patients previously treated with ruxolitinib and with a current diagnosis of intermediate-2 or high-risk primary myelofibrosis, post-polycythaemia vera myelofibrosis, or post-essential thrombocythaemia myelofibrosis
Intervention(s)	400 mg fedratinib
Comparator(s)	None
Indicate if study supports application for marketing authorisation	No
Indicate if study used in the economic model	No
Rationale if study not used in model	Is not used in the model due to being a single-armed study, with insufficient follow-up time, and did not report all relevant outcomes
Reported outcomes specified in the decision problem	▪ Overall survival
All other reported outcomes	▪ Treatment duration ▪ Treatment outcomes

SACT = Systemic Anti-Cancer Therapy.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 FREEDOM-2

FREEDOM-2 was a phase 3, multicentre, open-label, randomised study that evaluated the efficacy and safety of a once daily 400-mg dose of fedratinib compared with BAT in 201 participants previously treated with ruxolitinib. The study included adult participants aged ≥ 18 years with a current diagnosis of intermediate-2 or high-risk PMF, post-PV MF, or post-ET MF.[36]

Participants included in FREEDOM-2 had been previously exposed to ruxolitinib with inadequate response as refractory or relapsed (< 10% SVR by magnetic resonance imaging [MRI] or < 30% decrease from baseline in spleen size by palpation or regrowth). Alternatively, participants treated with ruxolitinib for more than 28 days and experiencing a complication that requires either RBC transfusion or having grade ≥ 3 adverse events (AEs) of thrombocytopenia, anaemia, hematoma, and/or haemorrhage were also included in the study.[36]

The FREEDOM-2 trial design consisted of a screening period of up to 35 days with a 2:1 randomisation to fedratinib or BAT. For the fedratinib arm, the treatment phase consisted of 4 -week (28-day) cycles of fedratinib and a follow-up visit (approximately 30 days after the last dose of fedratinib). Participants could remain on fedratinib until disease progression or unacceptable toxicity. Participants were allowed to cross over from BAT to fedratinib after the sixth cycle response assessment, or earlier in the event of disease progression (confirmation of splenomegaly by MRI/computed tomography [CT] scan) (Figure 4).[36]

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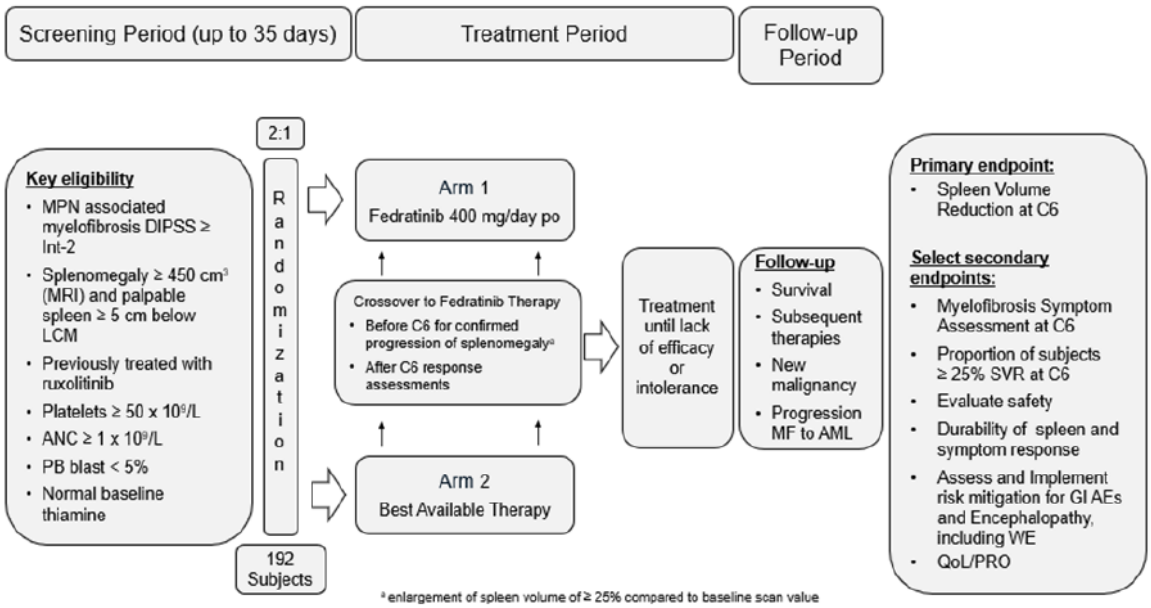
Figure 4. FREEDOM-2: study design



AE = adverse event; AML = acute myeloid leukaemia; ANC = absolute neutrophil count; C6 = cycle 6; DIPSS = Dynamic International Prognostic Scoring System; GI = gastrointestinal; Int-2 = intermediate-2; LCM = left costal margin; MF = myelofibrosis; MPN = myeloproliferative neoplasm; MRI = magnetic resonance imaging; PB = peripheral blood; PO = orally; PRO = patient-reported outcome; PV = polycythaemia vera; QOL = quality of life; SVR = spleen volume reduction; WE = Wernicke's encephalopathy.

Source: BMS data on file[36]

The primary outcome measure in FREEDOM-2 was spleen volume response rate, defined as the proportion of participants with a ≥ 35% SVR from baseline at the end of cycle 6 (EOC6) in the fedratinib and BAT arms. This was measured using an MRI or CT scan and assessed by blinded central review.[36] Splenomegaly is the main physical feature of myelofibrosis and the cause of many symptoms associated with the disease. As such, SVR is a key treatment goal in myelofibrosis (see Section B.2.6.1.2).

Secondary outcomes measured in FREEDOM-2 include[36]:

- Symptom response rate, proportion of participants with ≥ 50% reduction in total symptom score (TSS), measured by Myelofibrosis Symptom Assessment Form (MFSAF) at EOC6
- Spleen volume response rate by MRI or CT scan, proportion of participants who have ≥ 25% reduction in spleen volume at the EOC6 (RR25)
- Spleen response by palpation, ≥ 50% reduction in spleen size if spleen was > 10 cm below left costal margin (LCM) or non-palpable if spleen was palpable at 5 to 10 cm below the LCM
- Durability of spleen volume response, duration of ≥ 35% SVR by MRI/CT
- Durability of spleen response by palpation, ≥ 50% reduction in spleen size by palpation for participants with a palpable spleen at least 5 cm below LCM
- Durability of symptoms response, ≥ 50% reduction in TSS measured by MFSAF
- Spleen and disease progression-free survival (SDPFS)
- Overall survival (OS)
- HRQOL measured by EORTC QLQ-C30 domains
- Patient-reported outcomes (PROs) measured by EQ-5D-5L

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Exploratory outcomes measured in FREEDOM-2 include[36]:

- Time to spleen response by palpation: time from baseline to a ≥ 50% reduction in spleen size by palpation for participants with a palpable spleen at least 5 cm below the LCM at baseline
- Best spleen volume response rate during first 6 treatment cycles (BRR6): measured by MRI/CT scan during the first 6 treatment cycles and by MRI/CT scan from the start of study treatment to the end of study treatment
- Anaemia response: ≥ 2 g/dL increase in haemoglobin level in transfusion-independent participants or transfusion-dependent participants who become transfusion independent

A summary of the methodology of FREEDOM-2 is provided in Table 5.

Table 5. FREEDOM-2: summary of methodology

Study	NCT03952039 (FREEDOM-2)
Location	FREEDOM-2 was conducted in 103 sites in 16 countries, including 7 sites in the UK
Eligibility criteria for participants	Key inclusion criteria: ▪ Adult patients (≥ 18) who previously received ruxolitinib therapy and with DIPSS intermediate-2 or high-risk primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis ▪ Measurable splenomegaly during the screening period as demonstrated by spleen volume of ≥ 450 cm^3 by MRI or CT scan and by palpable spleen measuring ≥ 5 cm below LCM ▪ ECOG PS of 2 or less ▪ Measurable TSS (≥ 1) as measured by the MFSAF ▪ During the exposure to ruxolitinib, met at least one of the following criteria: – Treatment with ruxolitinib for ≥ 3 months with inadequate efficacy response (refractory) defined as < 10% SVR by MRI or < 30% decrease from baseline in spleen size by palpation or regrowth (relapsed) – Treatment with ruxolitinib for ≥ 28 days complicated by development of an RBC transfusion requirement (at least 2 units/month for 2 months) or grade ≥ 3 AEs of thrombocytopenia, anaemia, hematoma, and/or haemorrhage while on treatment with ruxolitinib. Key exclusion criteria: ▪ Received any chemotherapy, including ruxolitinib, within 14 days before the start of the study (except hydroxycarbamide, which was permitted within 1 day of initiation of fedratinib) ▪ A history of other malignancies ▪ Laboratory abnormalities ▪ History of previous encephalopathy (including Wernicke's encephalopathy) ▪ Other serious conditions, such as chronic liver disease, congestive heart failure, human immunodeficiency virus, infectious hepatitis B/C, or serious active infection ▪ Life expectancy of less than 6 months
Settings and locations where the data were collected	Steps taken to ensure the accuracy and reliability of the clinical study data included regular site monitoring visits to review study progress, investigator and participant adherence with the protocol requirements, and any emergent problems. Data were collected via eCRF. Data were verified electronically through use of programmed edit checks specified by the clinical team. An audit trail within the system tracked all changes made to the data. Protocol-required data were collected using electronic data capture for all parts of the study

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Study	NCT03952039 (FREEDOM-2)
	on eCRFs, which were completed by investigational site personnel and reviewed/approved by the investigator. Data for SAEs were submitted to Celgene-Impact using electronic SAE reports. Data review and quality control checks were implemented by Celgene-Impact and consisted of site monitoring visits guided by the site monitoring plan to review source documents against the eCRF and data validation checks of the eCRF and externally loaded data as per the established Data Review Plan. Data quality review was performed to ensure data completeness and data integrity.
Trial drugs	400 mg fedratinib was given orally, once daily. Fedratinib dose modifications were allowed based on observed toxicity to a 300 mg or 200 mg daily dose. Study treatment continued until disease progression or unacceptable toxicity.
Permitted and disallowed concomitant medication	Participants could not receive any other drug treatment of their disease while on study. Treatment with cytotoxic or immunomodulatory/suppressive therapy, including hydroxycarbamide or systemic corticosteroids (i.e., > 10 mg/day prednisone or equivalent for > 5 days), hydroxyurea, interferon-alpha, anagrelide, JAK inhibitors other than fedratinib, and aspirin (doses > 150 mg daily) was prohibited. Use of any other investigational agents during the study was prohibited.
Primary outcome (including scoring methods and timings of assessments)	The primary outcome, spleen volume response rate, was defined as the proportion of participants with a ≥ 35% SVR at EOC6 relative to baseline, as measured by MRI/CT scan. The MRI/CT scans were reviewed by an independent central imaging laboratory, where reviewers were blinded to the fedratinib doses.
Other outcomes used in the economic model/specified in the scope	Secondary efficacy assessments: ▪ Symptoms response rate, proportion of participants with ≥ 50% reduction in TSS, measured by MFSAF at EOC6 ▪ Spleen volume response rate by MRI or CT, proportion of participants who have ≥ 25% reduction in spleen volume at the EOC6 (RR25) ▪ Spleen response by palpitation, ≥ 50% reduction in spleen size if spleen was > 10 cm below LCM or non-palpable if spleen was palpable at 5-10 cm below the LCM ▪ Durability of spleen volume response, duration of ≥ 35% SVR by MRI/CT ▪ Durability of spleen response by palpation, ≥ 50% reduction in spleen size by palpation for participants with a palpable spleen at least 5 cm below LCM ▪ Durability of symptoms response, ≥ 50% reduction in TSS measured by MFSAF ▪ Spleen and disease progression-free survival (SDPFS) ▪ Overall survival ▪ HRQOL measured by EORTC QLQ-C30 domains ▪ PRO measured by EQ-5D-5L Key exploratory assessments: ▪ Time to spleen response by palpation, time from baseline to a ≥ 50% reduction in spleen size by palpation for participants with a palpable spleen at least 5 cm below the LCM at baseline. ▪ Best spleen volume response rate during the first 6 treatment cycles (BRR6), measured by MRI/CT scan during the first 6 treatment cycles and by MRI/CT scan from the start of study treatment to the end of study treatment. ▪ Anaemia response, ≥ 2 g/dL increase in haemoglobin level in transfusion-independent participants or transfusion-dependent participants who become transfusion independent.

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Study	NCT03952039 (FREEDOM-2)
Preplanned subgroups	Analyses of SVR and symptom response rate were measured in preplanned subgroups of: ▪ Demographic factors and baseline disease characteristics ▪ Platelet count/ haemoglobin count ▪ ECOG PS ▪ Hepatic and renal function

AE = adverse event; CT = computed tomography; DIPSS = Dynamic International Prognostic Scoring System; ECOG PS = Eastern Cooperative Oncology Group performance status; eCRF = electronic case report form; EOC6 = end of cycle 6; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Quality of Life of Cancer Patients (Core); HRQOL = health-related quality of life; JAK = Janus kinase; LCM = left costal margin; MFSAF = Myelofibrosis Symptom Assessment Form; MRI = magnetic resonance imaging; PRO = patient-reported outcome; QOL = quality of life; RBC = red blood cell; SAE = serious adverse event; SVR = spleen volume reduction; TSS = total symptom score; UK = United Kingdom.

Sources: BMS data on file[36]; BMS data on file[44]

B.2.3.1.1 Baseline demographics

The demographics and baseline disease characteristics in FREEDOM-2 are representative of a group of patients with advanced myelofibrosis and a high disease burden.

The demographic data matched what was anticipated based on the study design. The treatment groups did not differ significantly from one another. For the entire intention-to-treat (ITT) population, the median age was 70 years, ranging from 38 to 91 years. Most of the participants were White (n = 164 [81.6%]). Table 6 summarises the baseline characteristics in FREEDOM-2.

Table 6. FREEDOM-2: baseline characteristics (ITT population)

	Fedratinib (N = 134)	BAT (N = 67)
Median age, years (range)	70 (40-86)	68.0 (38-91)
Sex, n (%)		
Male	75 (56%)	30 (44.8%)
Female	59 (44%)	37 (55.2%)
Race, n (%)		
White	106 (79.1%)	58 (86.6%)
Asian	9 (6.7%)	5 (7.5%)
American Indian or Alaska Native	0 (0%)	1 (1.5%)
Unknown	19 (14.2%)	3 (4.5%)
Median weight, kg (range)	71.7 (43.0-112.2)	66.20 (45.5-108.0)
Disease type, n (%)		
Primary myelofibrosis	75 (56.0%)	35 (52.2%)
Post-polycythaemia vera	33 (24.6%)	21 (31.3%)
Post-essential thrombocythaemia	26 (19.4%)	11 (16.4%)
Risk status, n (%)[b]		
Intermediate-2	102 (76.1%)	51 (76.1%)
High risk	30 (22.4%)	16 (23.9%)
Missing	2 (1.5%)	0 (0.0%)
Median time since diagnosis, months (range)	43.40 (0.0-360.0)	57.70 (0.0-381.5)

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	Fedratinib (N = 134)	BAT (N = 67)
JAK2/CALR/MPL variant status, n (%)		
Mutant	119 (88.8%)	64 (95.5%)
Triple negative	3 (2.2%)	0 (0.0%)
Incomplete testing	12 (9.0%)	3 (4.5%)
RBC transfusion dependence status, n (%)[a]		
Yes	29 (21.6%)	11 (16.4%)
No	105 (78.4%)	56 (83.6%)
Platelet count (10^9/L)		
n	129	64
Median (range)	124.0 (30-1,715)	117.0 (29-846)
Haemoglobin (g/dL)		
n	134	67
Median (range)	93 (57-144)	94 (65-140)
ECOG PS, n (%)		
0	35 (26.1%)	20 (29.9%)
1	76 (56.7%)	35 (52.2%)
2	22 (16.4%)	11 (16.4%)
3	1 (0.7%)	1 (1.5%)
Constitutional symptoms[b]		
Yes	84 (62.7%)	42 (62.7%)
No	50 (37.3%)	25 (37.3%)
Median baseline spleen volume, mL (range)[c]	2,622.34 (498.2-8,909.4)	2,692.83 (383.1-8,514.8)
Median baseline spleen size, cm (range)[d]	16.00 (5.0-37.0)	15.00 (4.0-40.0)

BAT = best available therapy; CT = computed tomography; ECOG PS = Eastern Cooperative Oncology Group performance status; IPSS = International Prognostic Scoring System; IWG-MRT = International Working Group-Myeloproliferative Neoplasms Research and Treatment; ITT = intention to treat; JAK2 = Janus kinase 2; MPN-SAF = Myeloproliferative Neoplasm Symptom Assessment Form; MRI = magnetic resonance imaging; RBC = red blood cell.

Notes: Spleen volume was measured by MRI/CT scan and reviewed in a blinded fashion by a central imaging laboratory. Spleen size was measured by palpation (i.e., length in cm).

[a] RBC transfusion dependence at baseline was defined per revised IWG-MRT criteria 2013.

[b] A participant had constitutional symptoms if any of the symptoms were in the baseline MPN-SAF (> 10% weight loss in 6 months, night sweat, unexplained fever > 37.5 °C).

[c] Baseline spleen volume by MRI/CT scan based on central review.

[d] Below lower coastal region.

Source: BMS data on file[36]

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Prior myelofibrosis treatment

All 201 participants had received prior treatment with ruxolitinib over at least 3 months. The median time from the last ruxolitinib dose to the first dose of fedratinib was 21 days (minimum 3 days, maximum 2,671 days). Prior anticancer therapies other than ruxolitinib for MF were reported for 34 participants (16.9%). The compound reported most often was hydroxycarbamide (in 28 participants [13.9%]). Prior RBC transfusions were reported for 101 participants (50.2%) and prior platelet transfusions were reported for 8 (4.0%). There were no notable differences between the treatment groups. Red blood cell transfusion dependence at baseline was reported for 29 participants (21.6%) in the fedratinib group and 11 (16.4%) in the BAT group.[36]

Of the participants enrolled and treated in FREEDOM-2, 20.4% were intolerant to ruxolitinib, 27.9% had a loss of response to ruxolitinib, and 26.9% never responded to ruxolitinib.[45] A summary of the reasons for ruxolitinib discontinuation is provided in Table 7.

Table 7. FREEDOM-2: reasons for ruxolitinib discontinuation by investigator assessment (ITT population)

	Fedratinib (N = 134)	BAT (N = 67)	Total (N = 201)
Ruxolitinib AEs/intolerant, n (%)	27 (20.1%)	14 (20.9%)	41 (20.4%)
Loss of response	38 (28.4%)	18 (26.9%)	56 (27.9%)
Never responded	40 (29.9%)	14 (20.9%)	54 (26.9%)
Partial response	3 (2.2%)	5 (7.5%)	8 (4.0%)
Other: physician decision	5 (3.7%)	5 (7.5%)	10 (5.0%)
Other: protocol requirement for ruxolitinib discontinuation	14 (10.4%)	7 (10.4%)	21 (10.4%)

AE = adverse event; BAT = best available therapy; ITT = intention to treat.

Note: Intolerance: haematological toxicity (anaemia, thrombocytopenia, other), non-haematological toxicity.

Source: BMS data on file[45]

Patient summary by crossover status

All randomly assigned participants qualified for the ITT and safety populations, and were treated according to their randomisation.[36] As previously described, the study allowed for crossover from BAT to fedratinib after the sixth cycle response assessment, or earlier in the event of disease progression (confirmation of splenomegaly by MRI/CT scan), which aligns with the timing of assessment in clinical practice.[44] The number of participants per treatment group and population is presented in Table 8.

Table 8. FREEDOM-2: analysis population (ITT population)

Analysis population	Fedratinib (n = 134) n (%)	BAT (n = 67) n (%)	Total (n = 201) n (%)
ITT population[a]	134 (100.0)	67 (100.0)	201 (100.0)
Per-protocol population[b]	105 (78.4)	55 (82.1)	160 (79.6)
Symptom evaluable population[c]	121 (90.3)	62 (92.5)	183 (91.0)
Safety population[d]	134 (100.0)	67 (100.0)	201 (100.0)
Crossover efficacy population[e]	NA	46 (68.7)	46 (22.9)
Crossover safety population[f]	NA	46 (68.7)	46 (22.9)
HRQOL evaluable population[g]			

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Analysis population	Fedratinib (n = 134) n (%)	BAT (n = 67) n (%)	Total (n = 201) n (%)
EORTC QLQ-C30	105 (78.4)	50 (74.6)	155 (77.1)
EQ-5D-5L	103 (76.9)	52 (77.6)	155 (77.1)
PRO-CTCAE	97 (72.4)	49 (73.1)	146 (72.6)

BAT = best available therapy; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Quality of Life of Cancer Patients (Core); HRQOL = health-related quality of life; ITT = intention to treat; PRO = patient-reported outcome; PRO-CTCAE = Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events.

Notes: Percentages are based on the number of participants in the ITT population.

[a] All participants who were randomly assigned.

[b] All participants who received the treatment they were assigned to by randomisation, had no important violation of inclusion/exclusion criteria, and no other important protocol deviations that could impact on efficacy outcome.

[c] All participants who had been treated and had evaluable symptom assessments (i.e., non-zero total symptom score) at baseline and at least 1 after baseline.

[d] All participants who were administered at least 1 dose of study medication.

[e] All participants from the BAT arm who crossed over to the fedratinib arm.

[f] All participants from the BAT arm who crossed over to the fedratinib arm and received at least 1 dose of fedratinib.

[g] All participants who had an evaluable assessment of a given PRO/HRQOL measure at baseline and at least 1 evaluable assessment of a given PRO/HRQOL measure after baseline.

Source: BMS data on file[36]

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 FREEDOM-2

The primary objective of FREEDOM-2 was to compare the SVR at EOC6 in participants who received fedratinib versus those who received BAT. The primary outcome was spleen volume response rate, which was defined as the proportion of participants who had ≥ 35% SVR at EOC6 measured from baseline. The hypothesis was as follows:

$$H_0: RR_{FEDA} \leq RR_{BAT}$$

versus

$$H_a: RR_{FEDA} > RR_{BAT}$$

To consider the sample size needed for FREEDOM-2, data from JAKARTA-2 were used. In the JAKARTA-2 study, the reported response rate of fedratinib was approximately 35% for the per-protocol population. With the assumption of a 20% dropout rate, the response rate would be 28% based on the ITT population. Assuming a true ITT response rate (considering dropouts) in the BAT arm of 10%, 192 participants will yield approximately 90% power at a one-sided significance level of 0.025.[44]

The primary analysis for spleen volume response rate as measured by MRI/CT is based on the ITT population. The data cutoff for response rate occurred when the last randomly assigned participant had completed 6 cycles of fedratinib or BAT. Participants with a missing measurement of spleen volume at EOC6, including those who meet the criteria for progression of splenomegaly before EOC6, were considered as non-responders. For crossover participants, only data before crossover were included.[44]

A Cochran-Mantel-Haenszel (CMH) test to adjust for planned stratification factors (spleen size by palpation, platelet counts, and refractory/relapsed or intolerance to ruxolitinib treatment) was performed to compare fedratinib to BAT at a one-sided 2.5% alpha level. The response rates and 95% confidence

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intervals (CIs) were provided for each arm, as well as for the difference in response rates and 95% CI of the difference for fedratinib to BAT.[44] Table 9 summarises the statistical analyses in FREEDOM-2.

Table 9. FREEDOM-2: summary of statistical analyses

Trial number (acronym)	NCT03952039 (FREEDOM-2)
Hypothesis objective	Fedratinib will improve SVR in patients with myelofibrosis who have been previously treated with ruxolitinib, compared with BAT
Statistical analysis	▪ Spleen responses were measured using MRI/CT and continuous variables were summarised using descriptive statistics (i.e., n, mean, median, SD, min, max) ▪ A one-sided significance level of α = 0.25 was used for hypothesis testing and CIs were calculated using the 2-sided 95% CI unless otherwise specified ▪ A CMH test to adjust for planned stratification factors
Sample size, power calculation	Assuming 28% in fedratinib arm and 10% in BAT arm achieved the primary endpoint of a ≥ 35% reduction in spleen volume from baseline, 192 evaluable participants were required to provide at least 90% power at a one-sided significance level of 0.
Data management, patient withdrawals	Data were collected via CRF and entered into the clinical database per Celgene Standard Operating Procedures. These data were electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data were brought to the attention of the clinical team and investigational site personnel. An audit trail within the system will track all changes made to the data. Withdrawal of an investigational product was reported as an AE.

AE = adverse event; BAT = best available therapy; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; CRF = case report form; CT = computed tomography; max = maximum; min = minimum; MRI = magnetic resonance imaging; n = number of observations; SD = standard deviation; SVR = spleen volume reduction.

Source: BMS data on file[44]

Further information regarding the participant flow in FREEDOM-2 is presented in Appendix D.

B.2.4.2 SACT data set

The SACT data set was an evaluation of real-world treatment efficacy of fedratinib in the CDF population. There were 75 applications for CDF funding of fedratinib for the treatment of disease-related splenomegaly or symptoms in myelofibrosis between 17 November 2021 and 31 October 2022 in the NHS England Blueteq database. After de-duplication, 67 unique patients were identified. One patient was then excluded because they received fedratinib before the drug was available through the CDF, 1 patient did not receive treatment, 4 patients died before treatment, and 7 patients were missing from SACT, resulting in 54 patients being included in the analysis.[46]

The included patients were then followed up through the National Disease Registration Service (NDRS) routinely collected SACT data to provide SACT treatment history. The efficacy outcomes presented in the NDRS NHS England report were treatment duration and OS.[46] Table 10 presents the clinical treatment criteria for patients included in the SACT data set as well as a summary of the methodology.[46] Table 11 presents the completeness of the key SACT variables collected.

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Table 10. SACT data set: summary of methodology

Study	SACT data set
Location	NHS England
Eligibility criteria for participants	Key inclusion criteria: ▪ The cycles of systemic anticancer therapy with fedratinib was prescribed by a consultant specialist specifically trained and accredited in the use of systemic anticancer therapy ▪ Adult patients diagnosed with primary myelofibrosis (also known as *chronic idiopathic myelofibrosis*), post-polycythaemia vera myelofibrosis, or post-essential thrombocythaemia myelofibrosis ▪ Patient's myelofibrosis has a risk category that is either intermediate-2 or high risk ▪ Patient has symptomatic disease-related splenomegaly and/or constitutional symptoms of myelofibrosis ▪ Patient has been previously treated with ruxolitinib ▪ Patient has an ECOG PS of 0 or 1 or 2 ▪ Patients must have thiamine (vitamin B1) levels tested both before and during fedratinib therapy and thiamine deficiency must be corrected before treatment starts and during fedratinib therapy ▪ In terms of active systemic therapy, fedratinib was being given as monotherapy ▪ Patient has not previously received fedratinib unless the patient has received fedratinib via a company early access scheme ▪ Fedratinib was to be continued until loss of clinical benefit or unacceptable toxicity or patient choice to stop treatment ▪ Clinician was aware fedratinib has clinically important interactions with drugs which affect the CYP3A4, CYP2C19, and CYP2D6 enzyme systems ▪ A formal medical review as to how fedratinib was being tolerated and whether treatment with fedratinib should have continued or not will be scheduled to occur at least by the start of the third 4-weekly cycle of treatment ▪ When a treatment break of more than 6 weeks beyond the expected 4-weekly cycle length was needed, a treatment break approval form will need to be completed to restart treatment, including indicating as appropriate if the patient had an extended break because of COVID-19 ▪ Fedratinib is to be otherwise used as set out in its summary of product characteristics
Settings and locations where the data were collected	Through the NHS England Blueteq system (for the period of November 2021 through October 2022), identified patients were then followed up through NDRS's routinely collected SACT data to provide SACT treatment history.
Trial drugs	400 mg fedratinib Study treatment continued until disease progression or unacceptable toxicity
Permitted and disallowed concomitant medication	In terms of active systemic therapy, fedratinib was being given as monotherapy
Primary outcome (including scoring methods and timings of assessments)	▪ Treatment duration – Treatment duration is calculated from the start of a patient's treatment to their last known treatment date in SACT. ▪ OS – OS is calculated from the CDF treatment start date, not the date of a patient's cancer diagnosis. Survival from the treatment start date is calculated using the patient's earliest treatment date, and the patient's date of death or the date the patient was traced for their vital status.

CDF = cumulative distribution function; ECOG PS = Eastern Cooperative Oncology Group performance status; NDRS = National Disease Registration Service; NHS = National Health Service; OS = overall survival; SACT = Systemic Anti-Cancer Therapy.

Source: NHS England data on file[46]

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Table 11. SACT data set: completeness of key data variables for the fedratinib cohort (N = 54)

Variable	Completeness (%)
Primary diagnosis	100%
Date of birth (used to calculate age)	100%
Gender	100%
Start date of regimen	100%
Start date of cycle	100%
Administration date	98%
Performance status at start of regimen	52%
Outcome summary of why treatment was stopped	89%
Diagnosis of primary myelofibrosis	100%
Risk category	100%
Previously treated with ruxolitinib	100%

SACT = Systemic Anti-Cancer Therapy.

Source: NHS England data on file[46]

B.2.4.2.1 Patient characteristics

The median age of the 54 patients receiving fedratinib for the treatment of disease-related splenomegaly or symptoms of myelofibrosis was 72 years. The median age in males and females was 73 and 72 years, respectively. Table 12 presents patient characteristics in the SACT data set.

Table 12. SACT data set: patient characteristics

Variable	N	%
Gender		
Male	41	76%
Female	13	24%
Age		
< 40	2	4%
40 to 49	2	4%
50 to 59	4	7%
60 to 69	14	26%
70 to 79	26	48%
80+	6	11%
Performance status at the start of regimen		
0	8	15%
1	15	28%
2	5	9%
3	0	0%
4	0	0%
Missing	26	48%
Diagnosis of primary myelofibrosis		
Primary myelofibrosis	30	56%

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Variable	N	%
Post-polycythaemia vera myelofibrosis	12	22%
Post-essential thrombocythaemia myelofibrosis	12	22%
Risk category		
Intermediate-2	37	69%
High risk	17	31%
Previously treated with ruxolitinib		
Disease progression on ruxolitinib	41	76%
Patient intolerance of ruxolitinib	13	24%

SACT = Systemic Anti-Cancer Therapy.

Note: Figures may not sum to 100% due to rounding.

Source: NHS England data on file[46]

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

B.2.5.1 FREEDOM-2

This study is generally considered a high-quality study, being conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The rights, safety, and well-being of the study participants were the most important consideration and prevailed over the interests of science and society. The protocol, amendments, and participant informed consent received appropriate approval by the Institutional Review Board/Independent Ethics Committee before initiation of study at the site.[36]

Measures to minimise bias were considered in the study design and third parties were used for critical activities, such as[36]:

- Randomised treatment allocation
- Prespecified criteria for dose modification, dose adjustment, and management of nausea, vomiting, diarrhoea, and encephalopathy including Wernicke's encephalopathy
- Use of centralised vendors: interactive response technology (IRT), central laboratories
- Selected study procedures performed in a blinded manner: MRIs/CTs relevant for the primary efficacy outcome, and further efficacy outcomes
- Supervision of the conduct of the trial by a Steering Committee, presided over by the coordinating Principal Investigator and representative Regional Investigators from participating countries

B.2.6 Clinical effectiveness results of the relevant studies

B.2.6.1 FREEDOM-2

B.2.6.1.1 Overview

The efficacy of fedratinib over BAT in patients who have been treated with ruxolitinib has been demonstrated in FREEDOM-2[36] and is supported by similar efficacy in the single-armed FREEDOM trial, the JAKARTA-2 trial, and the JAK inhibitor–naive patient population from JAKARTA.[41,47]

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The results for the primary endpoint (≥ 35% SVR at EOC6), as well as the results for both of the 2 key secondary endpoints (≥ 50% reduction in TSS at EOC6, ≥ 25% SVR at EOC6), proved superiority for fedratinib over BAT while controlling the family-wise Type I error rate at a one-sided significance level of 0.025.

In the ITT population of FREEDOM-2, 35.8% of participants receiving fedratinib and 6% receiving BAT achieved the primary outcome of spleen volume response rate defined as ≥ 35% SVR at EOC6. Similarly, 34.1% of participants receiving fedratinib and 16.9% receiving BAT achieved the key secondary outcome of symptom response rate defined as ≥ 50% reduction in TSS at EOC6. Furthermore, 47% of participants receiving fedratinib and 13.4% receiving BAT achieved the key secondary outcome of spleen volume response rate defined as ≥ 25% SVR at EOC6. An overview of the results for key outcomes from FREEDOM-2 is provided in Table 13. Full trial results for the ITT FREEDOM-2 population are presented in subsequent sections. Supporting results from JAKARTA, JAKARTA-2, and FREEDOM are provided in Appendix D.

Table 13. FREEDOM-2: overview of fedratinib efficacy (ITT population)

Primary outcome	**Measure**	**Fedratinib (n = 134)**	**BAT (n = 67)**
Spleen volume response rate	≥ 35% SVR at EOC6,[a] n (%); (95% CI)[b]	48 (35.8); (27.7-44.6)	4 (6.0); (1.7-14.6)
Key secondary outcome	**Measure**	**Fedratinib (n = 126)**	**BAT (n = 65)**
Symptom response rate at EOC6	≥ 50% reduction in TSS at EOC6,[a] n (%); (95% CI)[b]	43 (34.1); (25.9-43.1)	11 (16.9); (8.8-28.3)
Key secondary outcome	**Measure**	**Fedratinib (n = 134)**	**BAT (n = 67)**
Spleen volume response rate	≥ 25% SVR at EOC6,[a] n (%); (95% CI)[b]	63 (47.0); (38.3-55.8)	9 (13.4); (6.3-24.0)

BAT = best available therapy; CI = confidence interval; EOC6 = end of cycle 6; ITT = intention to treat; SVR = spleen volume reduction; TSS = total symptom score.

[a] Participants with missing assessment at EOC6, including those who met the criteria for progression of splenomegaly before EOC6, were considered non-responders. They were included in the denominator.

[b] The 2-sided 95% CI was based on the exact Clopper-Pearson method.

Source: BMS data on file[36]

B.2.6.1.2 Primary outcome: spleen volume response rate (≥ 35% SVR) at EOC6

Treatment with fedratinib is associated with a significant spleen volume response rate, with 35.8% of participants achieving ≥ 35% SVR at EOC6 compared with 6.0% of participants on BAT. Superiority of fedratinib was proven in the stratified analysis based on electronic case report form (eCRF) data and based on IRT data, as well as in the unstratified analysis. After imputation of missing data, the percentage of participants with ≥ 35% SVR at EOC6 was 43.3% in the fedratinib group and 9.0% in the BAT group (Table 14).[36]

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Table 14. FREEDOM-2: spleen volume response rates at EOC6 (≥ 35% SVR) by MRI or CT scan (ITT population)

Response	Fedratinib (N = 134)	BAT (N = 67)
Participants with ≥ 35% SVR at EOC6,[a] n (%); (95% CI)[b]	48 (35.8%); (27.7-44.6)	4 (6.0%); (1.7-14.6)
Stratified analysis, based on eCRF[c] Difference in proportion (95% CI)[d] *P* value	29.6 (19.9-39.4) < 0.0001	
Stratified analysis, based on IRT[c] Difference in proportion (95% CI)[d] *P* value	29.6 (19.9-39.3) < 0.0001	
Unstratified analysis[e] Difference in proportion (95% CI)[d] *P* value	29.9 (19.9-39.8) < 0.0001	
Participants with ≥ 35% reduction in spleen volume at EOC6, missing data imputation,[f] n (%); (95% CI)	58 (43.3); (34.1-52.5)	6 (9.0); (1.1-17.0)
Stratified analysis, based on eCRF[c] Difference in proportion (95% CI)[d] *P* value	34.3 (22.5-46.0) < 0.0001	

BAT = best available therapy; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; CT = computed tomography; eCRF = electronic case report form; EOC6 = end of cycle 6; IRT = interactive response technology; ITT = intention to treat; MRI = magnetic resonance imaging; SVR = spleen volume reduction.

[a] Participants with missing assessment at EOC6, including those who met the criteria for progression of splenomegaly before EOC6, were considered non-responders. They were included in the denominator.

[b] The 2-sided 95% CI was based on the exact Clopper-Pearson method.

[c] The stratified *P* value was one-sided based on CMH test using the Greenland and Robins method to adjust for stratification factors: spleen size by palpation and platelet counts. The third stratification factor 'refractory/relapsed or intolerance to ruxolitinib treatment' was dropped due to small cell count issue.

[d] The 95% CI of the difference was based on Greenland and Robins method.

[e] The unstratified *P* value was one-sided based on the z-test with an unpooled estimate of variance.

[f] For participants with missing assessment at EOC6, data were imputed using multiple imputation methods. Thirty imputed data sets were created. The proportion with 95% CI for each arm and the difference in proportion with 95% CI were calculated for each imputed data set and combined using Rubin's rules. The number of responders was back-calculated from the pooled adjusted response rate.

Source: BMS data on file[36]

In the ITT population, when considering individual changes in spleen volume for participants with measurements at baseline and EOC6, all participants except 5 in the fedratinib arm compared with 14 in the BAT arm showed a reduction in volume (Figure 5).[36]

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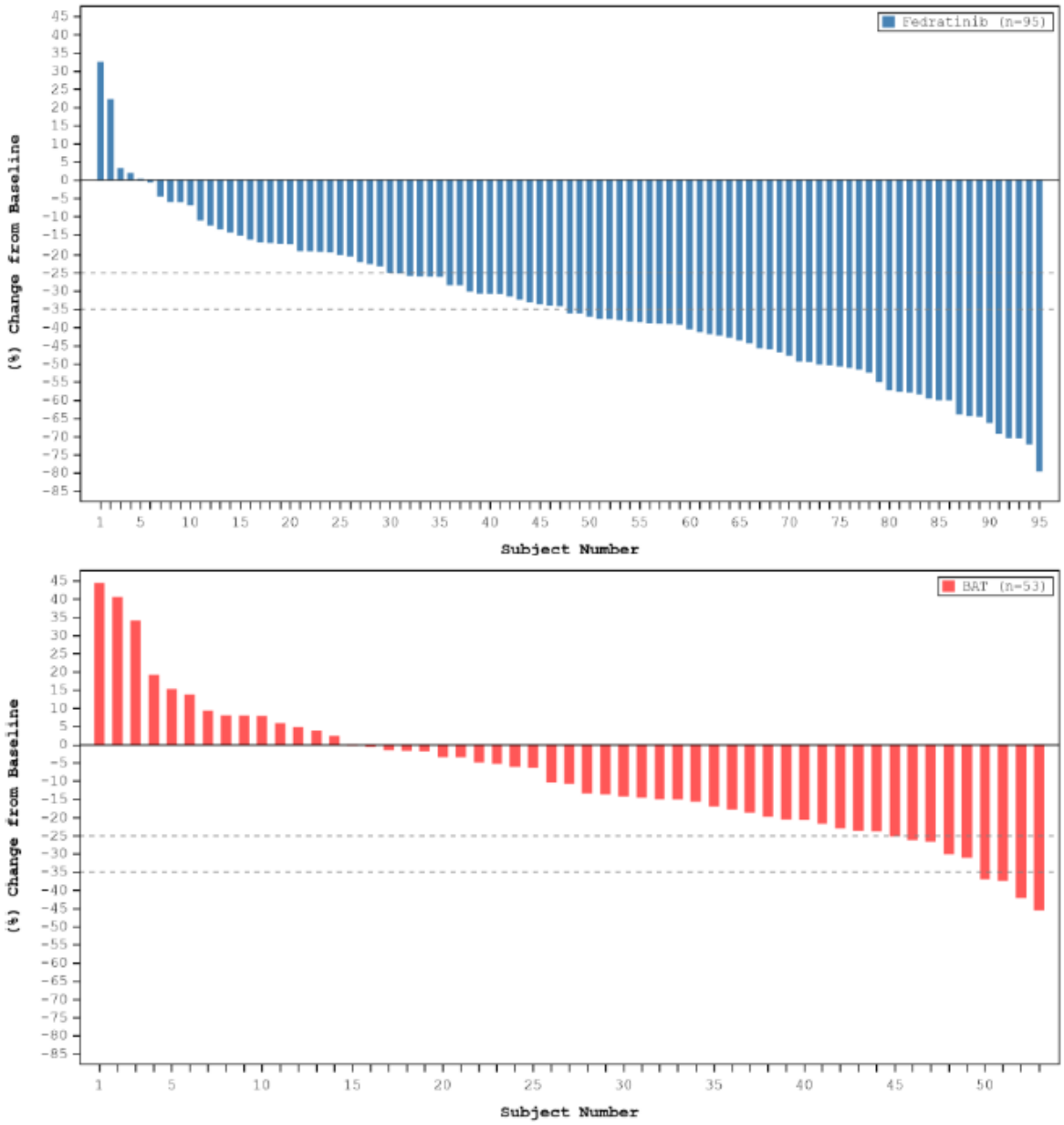
Figure 5. FREEDOM-2: percentage change in spleen volume from baseline to EOC6 in participants with MRI/CT scan at EOC6 (ITT population)



CT = computed tomography; EOC6 = end of cycle 6; ITT = intention to treat; MRI = magnetic resonance imaging.

Note: Each bar represents a participant with both baseline and post-baseline results. The dotted lines represent the 25% and 35% change from baseline.

Source: BMS data on file[36]

Additional analyses of spleen volume response rate (≥ 35% SVR)

The analysis of the primary efficacy endpoint was repeated based on data at EOC3. The advantage for fedratinib was supported by the results (Table 15).[36]

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Table 15. FREEDOM-2: spleen volume response rates at EOC3 (≥ 35% SVR) by MRI or CT scan (ITT population)

Response	Fedratinib (N = 134)	BAT (N = 67)
Participants with ≥ 35% reduction in spleen volume at EOC3, n (%); (95% CI)[a]	58 (43.3) (34.8-52.1)	4 (6.0); (1.7-14.6)
Stratified analysis, based on eCRF[b] Difference in proportion (95% CI)[c] *P* value	36.8 (26.9-46.8) < 0.0001	
Stratified analysis, based on IRT[b] Difference in proportion (95% CI)[c] *P* value	37.1 (27.4-46.9) < 0.0001	
Unstratified analysis[d] Difference in proportion (95% CI)[c] *P* value	37.3 (27.2-47.4) < 0.0001	

BAT = best available therapy; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; CT = computed tomography; eCRF = electronic case report form; EOC3 = end of cycle 3; IRT = interactive response technology; ITT = intention to treat; MRI = magnetic resonance imaging; SVR = spleen volume reduction.

[a] The 2-sided 95% CI was based on the exact Clopper-Pearson method.

[b] The stratified *P* value was one-sided based on CMH test using the Greenland and Robins method to adjust for stratification factors: spleen size by palpation and platelet counts. The third stratification factor 'refractory/relapsed or intolerance to ruxolitinib treatment' was dropped due to the small cell count issue.

[c] The 95% CI of the difference was based on Greenland and Robins method.

[d] The unstratified *P* value was one-sided based on the z-test with an unpooled estimate of variance.

Source: BMS data on file[36]

The treatment effect was generally consistent across subgroups. A possibly larger treatment effect was observed in the subgroup with platelet counts of 50 to < 100 × 10^9/L and the subgroup with ruxolitinib intolerance. In the BAT arm, most participants (n = 46) crossed over to fedratinib after EOC6. In participants remaining in the BAT arm, the SVR was at least 23%, as measured at EOC12 and EOC18. The mean percentage change in spleen volume from baseline is shown at every third cycle (see Figure 35).[36]

B.2.6.1.3 Secondary outcomes (key secondary outcomes)

Symptoms response rate

Symptoms response rate is a key secondary outcome, which requires at least 50% reduction in MF-associated symptoms, as measured by MFSAF TSS in the ITT population with non-zero baseline TSS at EOC6. This rate was reported by 43 participants (34.1%) in the fedratinib group and 11 (16.9%) in the BAT group. Superiority for fedratinib emerged from the stratified analyses, the unstratified analyses, and after imputation of missing data, as presented in Table 16.[36]

The completion rate at baseline of the MFSAF questionnaire was 100.0% in both treatment groups. At C6D1, the completion rate was 87.6% in the fedratinib group and 86.0% in the BAT group. Subsequent completion rates showed a steep decline because they included participants who had discontinued the study. At C6D1, the completion rate was 67.5% in the fedratinib group and 75.4% in the BAT group.[36]

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Table 16. FREEDOM-2: symptom response rate at EOC6 (ITT population with non-zero baseline TSS)

Response	Fedratinib (N = 126)	BAT (N = 65)
Participants with ≥ 50% reduction in TSS at EOC6,[a] n (%); (95% CI)[b]	43 (34.1); (25.9-43.1)	11 (16.9); (8.8-28.3)
Stratified analysis, based on eCRF[c] Difference in proportion (95% CI)[d] *P* value	17.1 (4.8-29.4) 0.0033	
Stratified analysis, based on IRT[c] Difference in proportion (95% CI)[d] *P* value	17.2 (4.9-29.5) 0.0030	
Unstratified analysis[e] Difference in proportion (95% CI)[d] *P* value	17.2 (4.9-29.5) 0.0031	
Participants with ≥ 50% reduction in TSS at EOC6, missing data imputation,[f] n (%); (95% CI)	58 (45.9); (36.5-55.3)	16 (25.2); (13.1-37.3)
Stratified analysis, based on CRF[c] Difference in proportion (95% CI)[d] *P* value	20.7 (5.5-35.8) 0.0037	

BAT = best available therapy; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; CRF = case report form; eCRF = electronic case report form; EOC6 = end of cycle 6; IRT = interactive response technology; ITT = intention to treat; TSS = total symptom score.

[a] Participants with missing assessment at EOC6, including those who met the criteria for progression of splenomegaly before EOC6, were considered non-responders. However, they were included in the denominator.

[b] The 2-sided 95% CI was based on the exact Clopper-Pearson method.

[c] The stratified *P* value was one-sided based on CMH test using the Greenland and Robins method to adjust for stratification factors: spleen size by palpation and platelet counts. The third stratification factor 'refractory/relapsed or intolerance to ruxolitinib treatment' was dropped due to the small cell count issue.

[d] The 95% CI of the difference was based on the Greenland and Robins method.

[e] The unstratified *P* value was one-sided based on z-test with unpooled estimate of variance.

[f] Participants with missing TSS assessment at EOC6 were imputed using multiple imputation methods. Thirty imputed data sets were created. The proportion with 95% CI for each arm and the difference in proportion with 95% CI were calculated for each imputed data set and combined using Rubin's rules. The number of responders was back-calculated from the pooled adjusted response rate.

Source: BMS data on file[36]

Spleen volume response rate, volume reduction ≥ 25%

The percentage of participants with ≥ 25% SVR at EOC6 was 47.0% in the fedratinib group and 13.4% in the BAT group. Superiority of fedratinib over BAT was shown in both stratified analyses, in the unstratified analysis, and after imputation of missing data (Table 17).[36]

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Table 17. FREEDOM-2: spleen volume response rate at EOC6 (≥ 25% SVR) by MRI or CT scan (ITT population)

Response	Fedratinib (N = 134)	BAT (N = 67)
Participants with ≥ 25% reduction in spleen volume at EOC6,[a] n (%); (95% CI)[b]	63 (47.0); (38.3-55.8)	9 (13.4); (6.3-24.0)
Stratified analysis, based on eCRF[c] Difference in proportion (95% CI)[d] *P* value	33.5 (21.9-45.1) < 0.0001	
Stratified analysis, based on IRT[c] Difference in proportion (95% CI)[d] *P* value	33.3 (21.6-44.9) < 0.0001	
Unstratified analysis[e] Difference in proportion (95% CI)[d] *P* value	33.6 (21.8-45.3) < 0.0001	
Participants with ≥ 25% reduction in spleen volume at EOC6, missing data imputation,[f] n (%); (95% CI)	80 (60.1); (50.9-69.2)	12 (18.2); (8.4-28.1)
Stratified analysis, based on CRF[c] Difference in proportion (95% CI)[d] *P* value	41.8; (28.5-55.1) < 0.0001	

BAT = best available therapy; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; CRF = case report form; CT = computed tomography; eCRF = electronic case report form; EOC6 = end of cycle 6; IRT = interactive response technology; ITT = intention to treat; MRI = magnetic resonance imaging; SVR = spleen volume reduction.

[a] Participants with missing assessment at EOC6, including those who met the criteria for progression of splenomegaly before EOC6, were considered non-responders. However, they were included in the denominator.

[b] The 2-sided 95% CI was based on the exact Clopper-Pearson method.

[c] The stratified *P* value was one-sided based on CMH test using the Greenland and Robins method to adjust for stratification factors: spleen size by palpation and platelet counts. The third stratification factor 'refractory/relapsed or intolerance to ruxolitinib treatment' was dropped due to the small cell count issue.

[d] The 95% CI of the difference was based on the Greenland and Robins method.

[e] The unstratified *P* value was one-sided based on z-test with unpooled estimate of variance.

[f] For participants with missing assessment at EOC6, data were imputed using multiple imputation methods. Thirty imputed data sets were created. The proportion with 95% CI for each arm and the difference in proportion with 95% CI were calculated for each imputed data set and combined using Rubin's rules. The number of responders was back-calculated from the pooled adjusted response rate.

Source: BMS data on file[36]

B.2.6.1.4 Secondary outcomes (other secondary outcomes)

Spleen response rate by palpation

A spleen response according to the International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) 2013 criteria was found by palpation at EOC6 in 38 participants (28.4%) in the fedratinib group and in 5 (7.7%) in the BAT group. The difference in the percentage was 19.9 (95% CI, 10.0-29.7) (Table 18).[36]

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Table 18. FREEDOM-2: spleen volume response rate by palpation

Response	Fedratinib (N = 134)	BAT (N = 65)[a]
Participants with spleen response by palpation at EOC6, n (%); (95% CI)[b]	38 (28.4); (20.9-36.8)	5 (7.7); (2.5-17.0)
Difference fedratinib: BAT (%) (95% CI for difference)[c]	19.9 (10.0-29.7)	

BAT = best available therapy; CI = confidence interval; EOC6 = end of cycle 6; LCM = left costal margin.

[a] In 2 participants in the BAT group and no participant in the fedratinib group, spleen size at baseline was < 5 cm at LCM.

[b] Two-sided 95% CI was based on the exact Clopper-Pearson method.

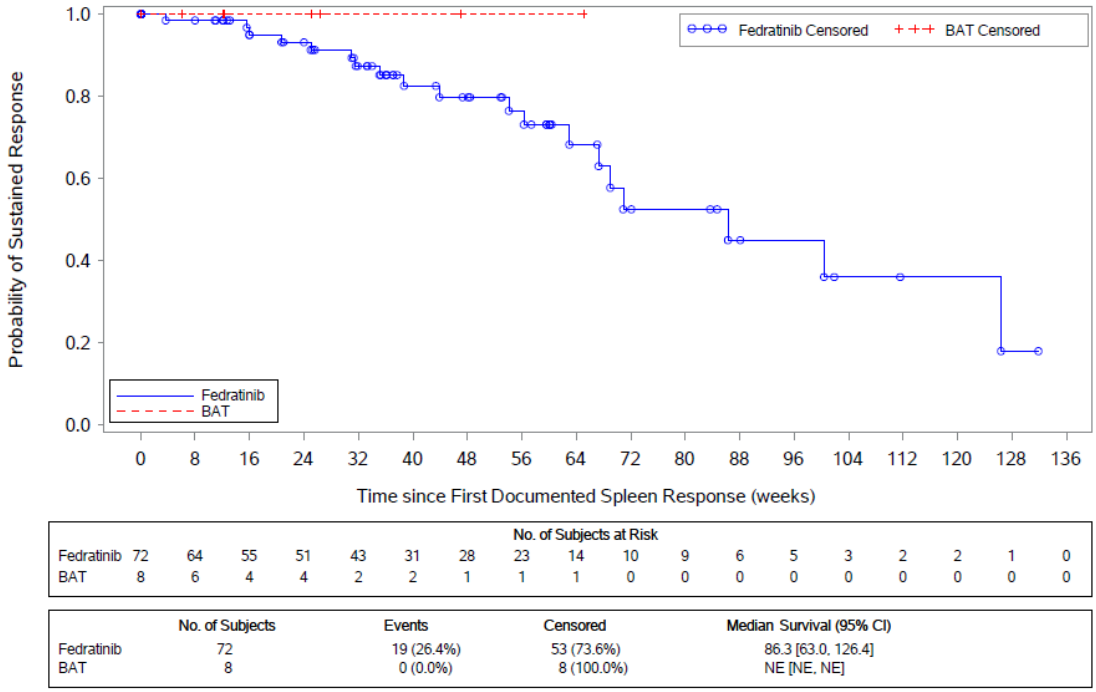
[c] The 95% CI of the difference was based on the Greenland and Robins method.

Source: BMS data on file[36]

Durability of spleen response by MRI/CT scan

In the ITT analysis, based on a median follow-up time of 36.1 (range, 0.1-131.9) weeks for the fedratinib group and 18.65 (range, 0.1-65.1) weeks for the BAT group, a Kaplan-Meier (KM) analysis yielded a median durability of spleen volume response by MRI/CT scan of 86.3 weeks in the fedratinib group. Median durability in the BAT group was not estimable (NE) (ITT analysis). Among 72 participants in the fedratinib group with spleen volume response at any time, an event relevant for this analysis was reported for 19 participants (26.4%). Data for the other 53 participants (73.6%) in the fedratinib group were censored. In the BAT group, 8 participants had a spleen volume response at any time. None of these participants had an event relevant for this analysis so that data for all 8 participants was censored. The durability of the spleen volume response by MRI/CT scan is provided as KM plots in Figure 6.

Figure 6. FREEDOM-2: Kaplan-Meier plot of durability of spleen volume response by MRI/CT scan (ITT population)



BAT = best available therapy; CI = confidence interval; CT = computed tomography; ITT = intention to treat; MRI = magnetic resonance imaging; NE = not estimable.

Source: BMS data on file[48]

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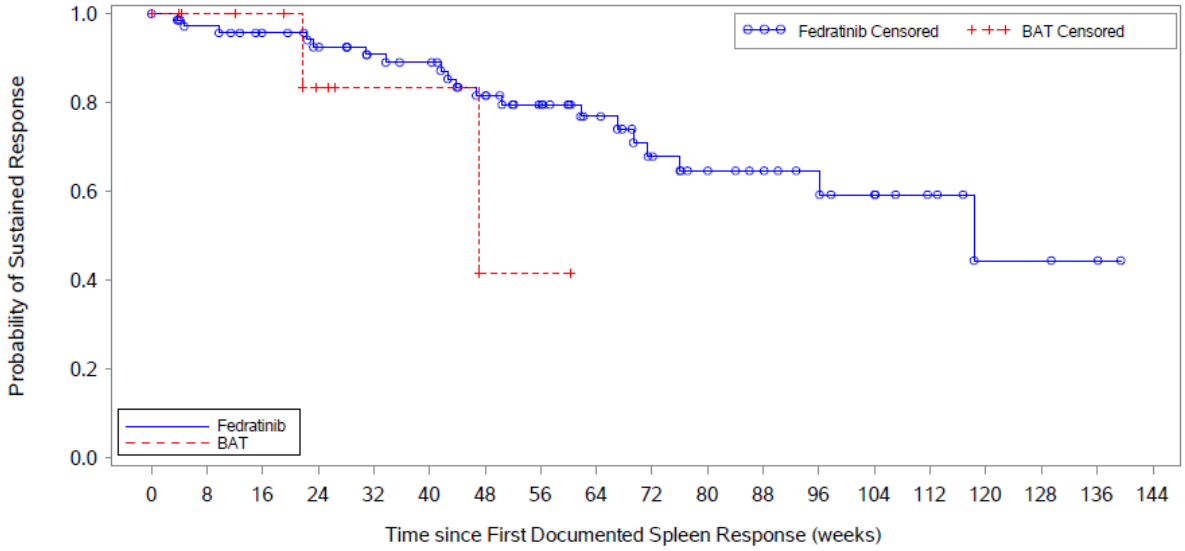
Durability of spleen response by palpation

Based on a median follow-up time of 56.10 (range, 3.7-139.4) weeks for the fedratinib group and 21.70 (range, 3.9-60.3) weeks for the BAT group, a KM analysis yielded a median durability of spleen response by palpation of 118.3 (95% CI, 76.0-NE) weeks in the fedratinib group and 47.1 (95% CI, 21.7-NE) weeks in the BAT group (ITT analysis). Among 71 participants in the fedratinib group with spleen response by palpation at any time, an event relevant for this analysis was reported for 19 participants (26.8%). Data for the other 52 participants (73.2%) in the fedratinib group were censored. In the BAT group, 11 participants had a spleen response by palpation at any time. There were 2 participants (18.2%) who had an event relevant for this analysis so that data for the other 9 participants (81.8%) were censored. A KM plot of the durability of the spleen response by palpation is provided in Figure 7.[36,45,48]

Figure 7. FREEDOM-2: Kaplan-Meier plot of durability of spleen response by palpation (ITT population)



No. of Subjects at Risk

Fedratinib	71	67	62	58	52	50	43	36	28	22	18	15	12	10	6	3	3	2	0
BAT	11	9	8	4	2	2	1	1	0	0	0	0	0	0	0	0	0	0	0

	No. of Subjects	Events	Censored	Median Survival (95% CI)
Fedratinib	71	19 (26.8%)	52 (73.2%)	118.3 [76.0, NE]
BAT	11	2 (18.2%)	9 (81.8%)	47.1 [21.7, NE]

BAT = best available therapy; CI = confidence interval; ITT = intention to treat; NE = not estimable.

Source: BMS data on file[48]

Durability of symptoms response

Based on a median follow-up time of 11.50 (range, 0.1-102.1) weeks for the fedratinib group and 8.10 (range, 0.1-37.0) weeks for the BAT group, a KM analysis yielded a median durability of the symptom response of 12.1 (95% CI, 8.1-16.1) weeks in the fedratinib group and 10.1 (95% CI, 4.1-16.7) weeks in the BAT group (ITT analysis). Among 90 participants in the fedratinib group with symptoms response at any time, an event relevant for this analysis was reported for 70 participants (77.8%). In the BAT group, 32 participants had symptoms response at any time. There were 27 participants (84.4%) who had events relevant for this analysis. A KM plot of the durability of symptoms response is provided in Figure 8.[36,45,48]

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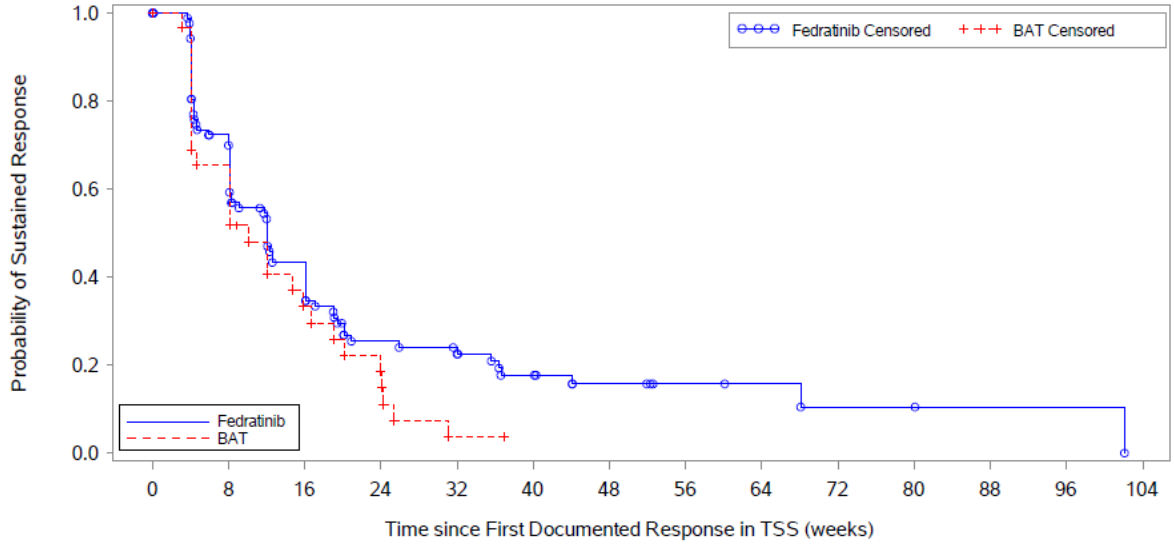
Figure 8. FREEDOM-2: Kaplan-Meier plot of durability of symptom response (ITT population)



No. of Subjects at Risk														
Fedratinib	90	61	35	18	16	11	7	4	3	2	2	1	1	0
BAT	32	19	9	6	1	0	0	0	0	0	0	0	0	0

	No. of Subjects	Events	Censored	Median Survival (95% CI)
Fedratinib	90	70 (77.8%)	20 (22.2%)	12.1 [8.1, 16.1]
BAT	32	27 (84.4%)	5 (15.6%)	10.1 [4.1, 16.7]

BAT = best available therapy; CI = confidence interval; ITT = intention to treat; TSS = total symptom score.

Source: BMS data on file[48]

Spleen and disease progression-free survival

Based on a median follow-up time of 46.20 (range, 0.1-148.9) weeks for the fedratinib group and 24.40 (range, 0.1-77.3) weeks for the BAT group, a KM analysis yielded a median time of SDPFS of 112.4 (95% CI, 75.0-NE) weeks in the fedratinib group and NE (95% CI, 30.4-NE) weeks in the BAT group (ITT analysis). Relevant events were reported for 42 participants (31.3%) in the fedratinib group and 12 (17.9%) in the BAT group. Figure 9 presents a KM plot of SDPFS.[36,45,48]

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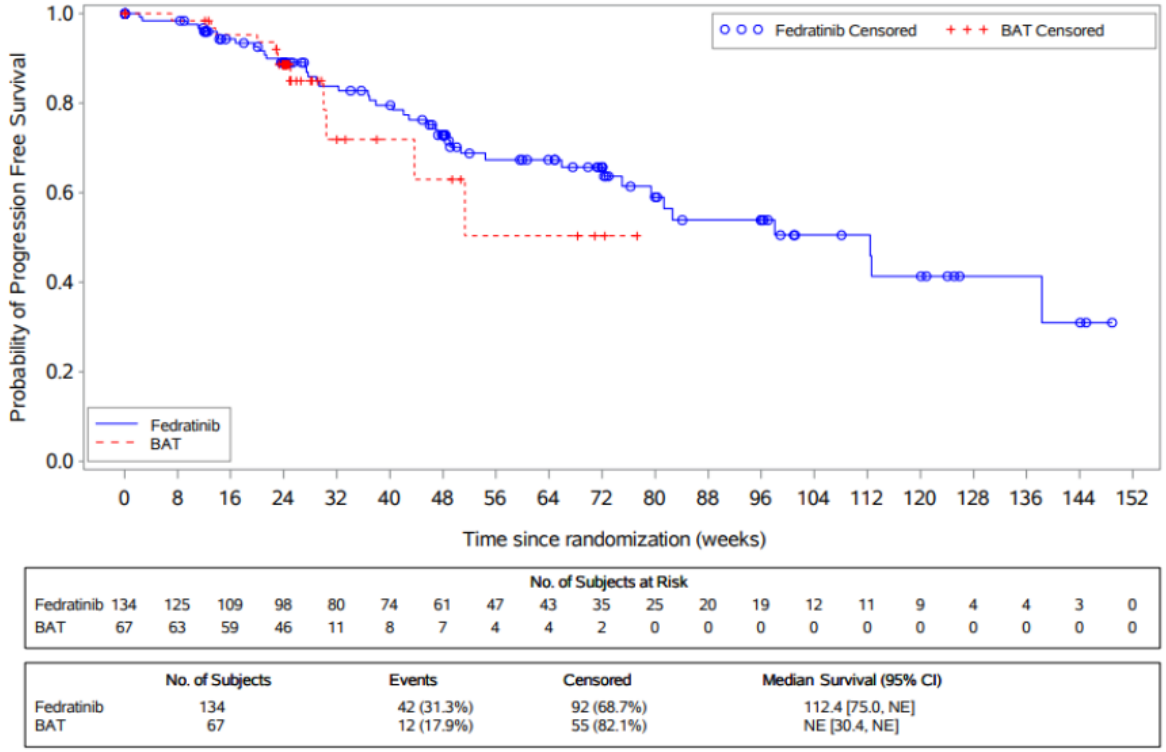
Figure 9. FREEDOM-2: Kaplan-Meier plot of spleen and disease progression-free survival (ITT population)



	No. of Subjects	Events	Censored	Median Survival (95% CI)
Fedratinib	134	42 (31.3%)	92 (68.7%)	112.4 [75.0, NE]
BAT	67	12 (17.9%)	55 (82.1%)	NE [30.4, NE]

BAT = best available therapy; CI = confidence interval; ITT = intention to treat; NE = not estimable.

Source: BMS data on file[36]

Overall survival

There are clear methodological issues that may result in an underestimate of OS for the fedratinib group, which means that the OS data need to be considered with caution. In the patient population that received BAT, nearly 70% crossed over to fedratinib, leaving very few participants in the BAT-only population, something the study was not powered for. Due to these limitations, crossover adjustments for OS have been explored and are presented in Section B.2.6.1.6.

In FREEDOM-2, based on a median follow-up time of 64.50 (range, 2.3-150.1) weeks for the fedratinib group and 63.70 (range, 1.9-146.0) weeks for the BAT group, a KM analysis yielded a median OS time of NE (95% CI, 112.6-NE) weeks in the fedratinib group and 124.6 (95% CI, 98.9-NE) weeks in the BAT group (ITT analysis). Over the full course of the study (full treatment period + crossover treatment period + follow-up period), death was reported for 43 participants (32.1%) in the fedratinib group and 18 (26.9%) in the BAT group. Figure 10 presents a KM plot of OS.[36,45,48]

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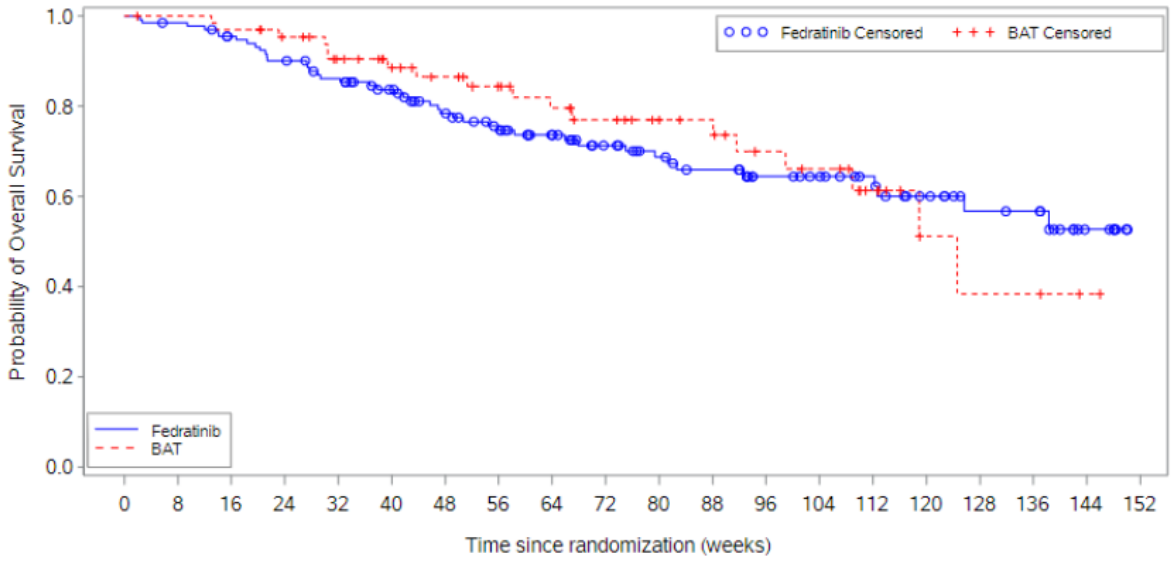
Figure 10. FREEDOM-2: Kaplan-Meier plot of overall survival (ITT population)



No. of Subjects at Risk

Fedratinib	134	131	124	117	109	99	87	77	68	58	51	46	38	35	30	23	17	16	6	0
BAT	67	66	64	60	53	47	42	37	33	29	25	23	18	16	10	4	3	3	1	0

	No. of Subjects	Events	Censored	Median Survival (95% CI)
Fedratinib	134	43 (32.1%)	91 (67.9%)	NE [112.6, NE]
BAT	67	18 (26.9%)	49 (73.1%)	124.6 [98.9, NE]

BAT = best available therapy; CI = confidence interval; ITT = intention to treat; NE = not estimable.

Source: BMS data on file[36]

EORTC QLQ-C30

At baseline, the completion of the EORTC QLQ-C30 questionnaires as reflected in the adherence rate was 100.0% in both treatment groups. At C6D1, the adherence rate was 90.5% in the fedratinib group and 89.1% in the BAT group. The completion rates declined more quickly over time due to participants discontinuing the study. At C6D1, the completion rate was 72.4% in the fedratinib group and 82.0% in the BAT group.[36]

At baseline, there was an imbalance in mean EORTC QLQ-C30 scores for most domains, demonstrating slightly better health status for participants in the fedratinib group than in the BAT group in all domains except for diarrhoea and appetite loss. The difference in baseline scores was clinically meaningful for the anaemia-related domains (physical functioning, fatigue, dyspnoea) as well as for the global health status, cognitive functioning, nausea and vomiting, pain, constipation, and financial difficulties, where the difference between the group means reached the threshold for small differences established in Cocks et al.[49] The results at baseline are presented in Table 19.[36]

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Table 19. FREEDOM-2: EORTC QLQ-C30 results at baseline (HRQOL evaluable population)

	Fedratinib (N = 105) mean (SD)	BAT (N = 50) mean (SD)
Global Health Status	49.7 (25.60)	43.3 (23.57)
Physical Functioning	61.1 (24.13)	55.6 (23.74)
Role Functioning	61.7 (34.51)	57.3 (34.36)
Emotional Functioning	71.7 (22.40)	66.5 (25.28)
Cognitive Functioning	79.8 (23.54)	75.0 (22.40)
Social Functioning	71.9 (30.25)	71.0 (30.27)
Fatigue	50.3 (29.52)	59.3 (27.18)
Nausea and Vomiting	8.1 (15.52)	12.0 (23.09)
Pain	33.2 (32.56)	42.7 (35.34)
Dyspnoea	36.5 (31.87)	40.7 (37.06)
Insomnia	40.3 (36.01)	42.7 (35.02)
Appetite Loss	34.6 (33.63)	30.7 (36.17)
Constipation	15.6 (24.92)	24.0 (31.62)
Diarrhoea	11.4 (22.09)	10.0 (22.59)
Financial Difficulties	7.3 (17.28)	11.3 (17.31)

BAT = best available therapy; HRQOL = health-related quality of life; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Quality of Life of Cancer Patients (Core); SD = standard deviation.

Source: BMS data on file[36]

Results by treatment group, cycle, and subscores (function, symptom domain scores) are provided below. Results are summarised for timepoints up to EOC6 due to potential crossover of participants in the BAT group to fedratinib. A ≥ 10-point change, as reported by Osoba et al.,[50] has been commonly used as a threshold to define a meaningful change at a group level (i.e., within-group change and between-group difference). To aid in interpretation, this threshold was used to highlight clinically meaningful change in the mean change from baseline.[36]

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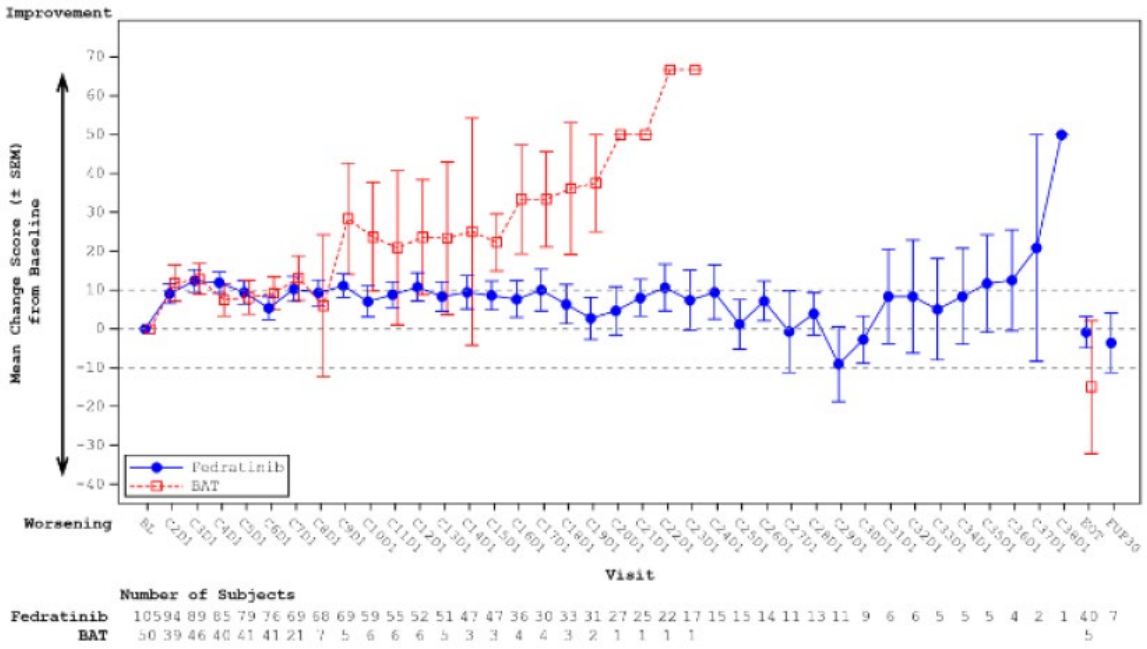
Global health status

In both treatment groups, there were increases from baseline in the mean scores for global health status, indicating improvement, during the treatment period through C6D1. Clinically meaningful change was observed at C3D1 and C4D1 for the fedratinib group and at C2D1 and C3D1 for the BAT group. At C6D1, the mean (SEM) change from baseline was 5.4 (26.02) for the fedratinib group and 9.1 (27.56) for the BAT group (Figure 11). Clinically meaningful HRQOL response by cycle results were supportive of these findings with more than half of the participants in both groups at most timepoints demonstrating clinically meaningful improvement.[36]

Figure 11. FREEDOM-2: EORTC QLQ-C30 Global Health Status/QOL scores (HRQOL evaluable population)



BAT = best available therapy; BL = baseline; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Quality of Life of Cancer Patients (Core); EOT = end of treatment; HRQOL = health-related quality of life; MID = minimally important difference; QOL = quality of life; SEM = standard error of mean.

Note: Horizontal reference lines indicate MID, considered a change of ± 10 points from baseline.

Source: BMS data on file[36]

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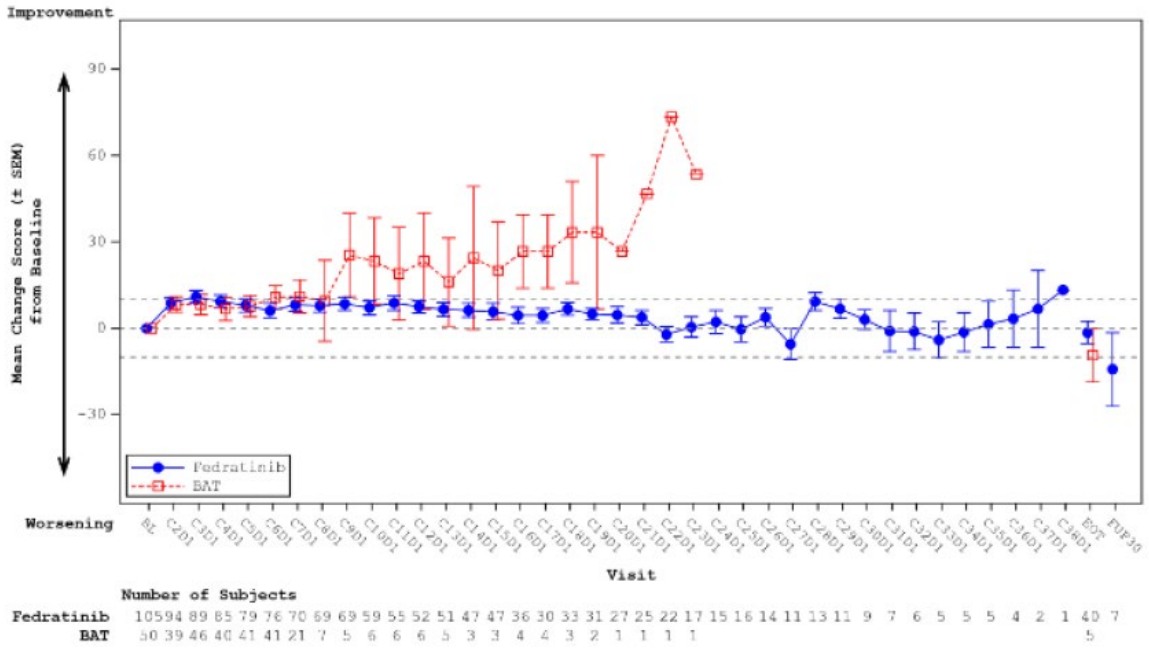
Physical functioning

In both treatment groups, there were increases from baseline in the mean scores for physical functioning, indicating improvement, during the treatment period through C6D1. Clinically meaningful change was observed at C3D1 for the fedratinib group and at C6D1 for the BAT group. At C6D1, the mean (SEM) change from baseline was 6.1 (21.22) for the fedratinib group and 10.7 (25.60) for the BAT group (Figure 12). Clinically meaningful HRQOL response results by cycle were supportive of these findings, with clinically meaningful improvement emerging for more than half of the participants in both groups at most timepoints.[36]

Figure 12. FREEDOM-2: EORTC QLQ-C30 Physical Functioning scores (HRQOL evaluable population)



BAT = best available therapy; BL = baseline; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Quality of Life of Cancer Patients (Core); EOT = end of treatment; HRQOL = health-related quality of life; MID = minimally important difference; SEM = standard error of mean.

Note: Horizontal reference lines indicated MID, considered a change of ± 10 points from baseline.

Source: BMS data on file[36]

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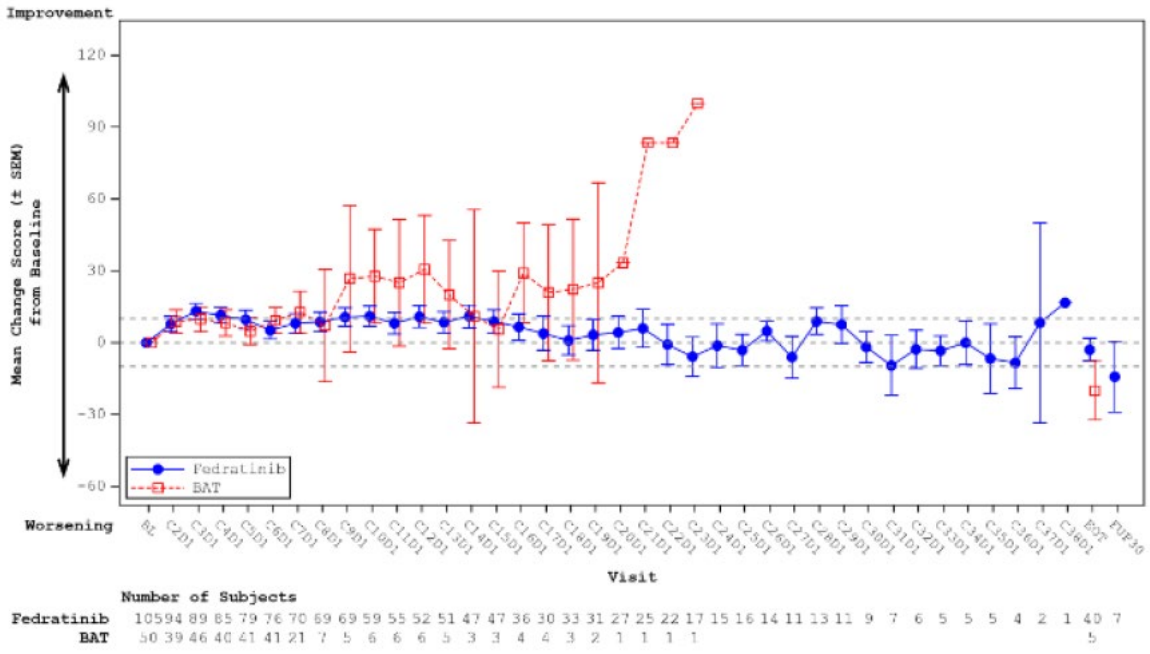
Role functioning

In both treatment groups, there were increases from baseline in the mean scores for role functioning, indicating improvement, during the treatment period through C6D1. Clinically meaningful change was observed at C3D1 and C4D1 for the fedratinib group and at no timepoint for the BAT group. At C6D1, the mean (SEM) change from baseline was 5.3 (31.88) for the fedratinib group and 9.3 (34.97) for the BAT group (Figure 13). Clinically meaningful HRQOL response by cycle results were supportive of these findings with more participants in both groups demonstrating clinically meaningful improvement than either no change or worsening in both groups at most timepoints.[36]

Figure 13. FREEDOM-2: EORTC QLQ-C30, Role Functioning scores (HRQOL evaluable population)



BAT = best available therapy; BL = baseline; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Quality of Life of Cancer Patients (Core); EOT = end of treatment; HRQOL = health-related quality of life; MID = minimally important difference; SEM = standard error of mean.

Note: Horizontal reference lines indicated MID, considered a change of ± 10 points from baseline.

Source: BMS data on file[36]

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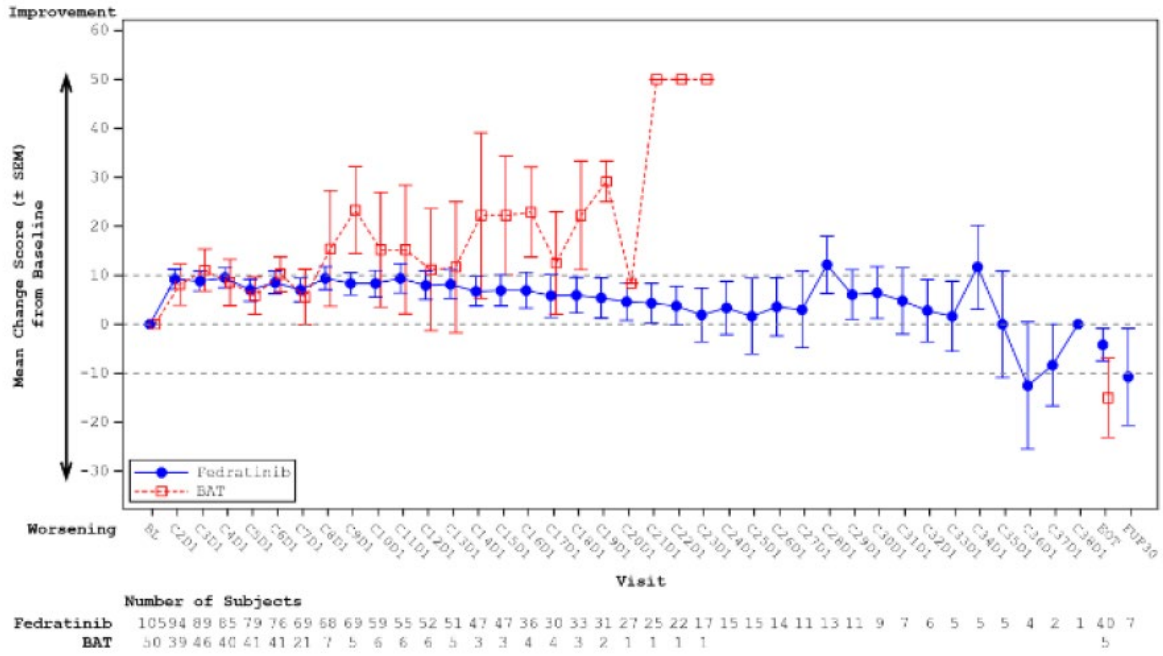
Emotional functioning

In both treatment groups, there were increases from baseline in the mean scores for emotional functioning, indicating improvement, during the treatment period through C6D1. The fedratinib group did not show clinically meaningful change at any timepoint, but the BAT group did at C3D1 and C6D1. At C6D1, the mean (SEM) change from baseline was 8.6 (19.81) for the fedratinib group and 10.2 (23.04) for the BAT group (Figure 14). Clinically meaningful HRQOL response results by cycle were supportive of these findings, with clinically meaningful improvement emerging for more participants in both groups than either no change or worsening at most timepoints.[36]

Figure 14. FREEDOM-2: EORTC QLQ-C30 Emotional Functioning scores (HRQOL evaluable population)



BAT = best available therapy; BL = baseline; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Quality of Life of Cancer Patients (Core); EOT = end of treatment; HRQOL = health-related quality of life; MID = minimally important difference; SEM = standard error of mean.

Note: Horizontal reference lines indicated MID, considered a change of ± 10 points from baseline.

Source: BMS data on file[36]

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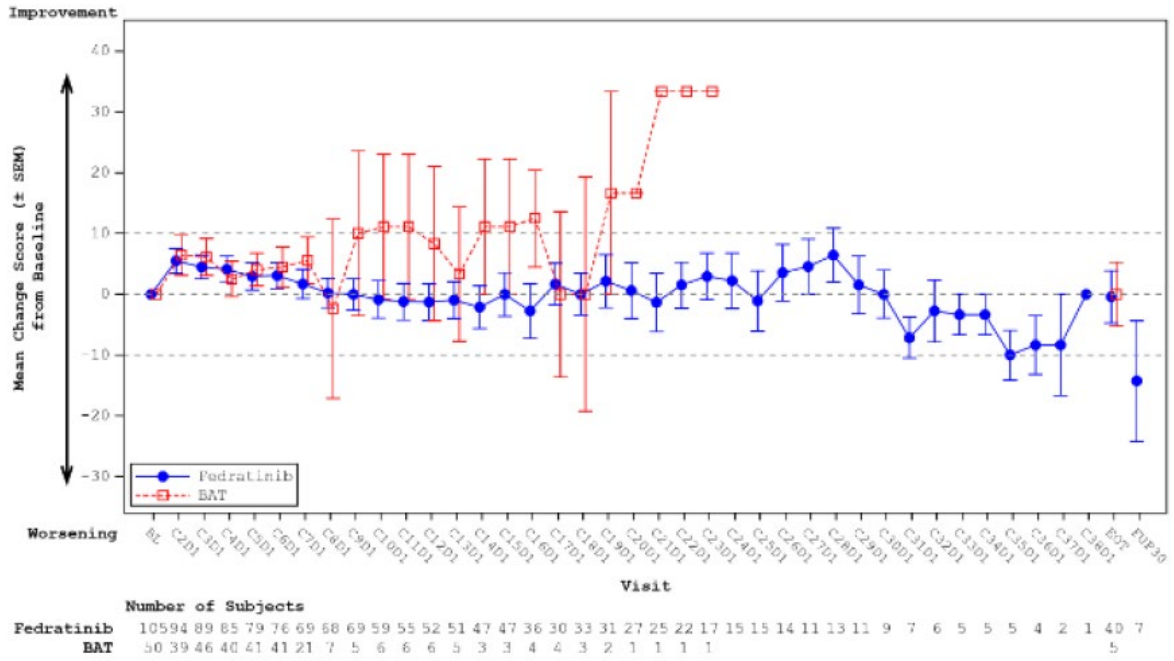
Cognitive functioning

In both treatment groups, there were increases from baseline in the mean scores for cognitive functioning, indicating improvement, during the treatment period through C6D1. However, neither treatment group showed clinically meaningful change at any timepoint. At C6D1, the mean (SEM) change from baseline was 3.1 (18.80) for the fedratinib group and 4.5 (21.09) for the BAT group (Figure 15). Clinically meaningful HRQOL response by cycle results were supportive of these findings, with most participants demonstrating clinically meaningful improvement or no change in both groups at most timepoints.[36]

Figure 15. FREEDOM-2: EORTC QLQ-C30 Cognitive Functioning scores (HRQOL evaluable population)



BAT = best available therapy; BL = baseline; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Quality of Life of Cancer Patients (Core); EOT = end of treatment; HRQOL = health-related quality of life; MID = minimally important difference; SEM = standard error of mean.

Note: Horizontal reference lines indicated MID, considered a change of ± 10 points from baseline.

Source: BMS data on file[36]

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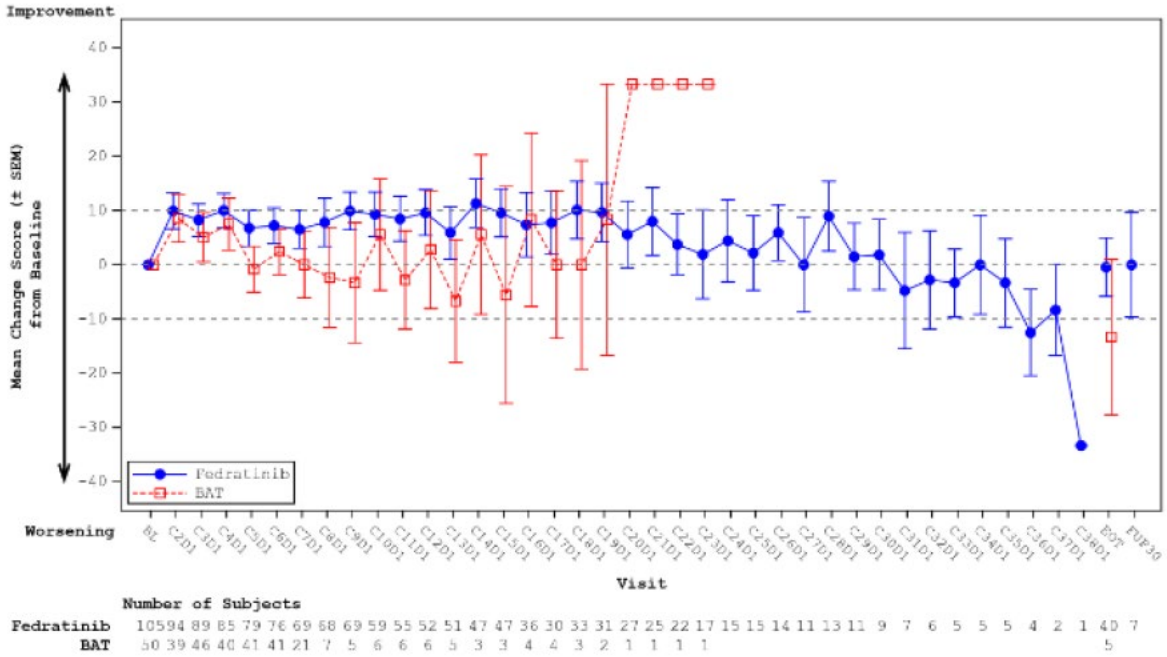
Social functioning

In both treatment groups, there were initial increases from baseline in the mean scores for social functioning, indicating improvement, in both treatment groups during the treatment period which continued through C6D1. The fedratinib group showed clinically meaningful change at C4D1 and the BAT group had no clinically meaningful change. At C6D1, the mean (SEM) change from baseline was 7.2 (28.72) for the fedratinib group and 2.4 (27.02) for the BAT group (Figure 16). Clinically meaningful HRQOL response results by cycle were supportive of these findings, with most participants demonstrating clinically meaningful improvement or no change in both groups at all timepoints.[36]

Figure 16. FREEDOM-2: EORTC QLQ-C30 Social Functioning scores (HRQOL evaluable population)



BAT = best available therapy; BL = baseline; QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Quality of Life of Cancer Patients (Core); EOT = end of treatment; HRQOL = health-related quality of life; MID = minimally important difference; SEM = standard error of mean.

Note: Horizontal reference lines indicated MID, considered a change of ± 10 points from baseline.

Source: BMS data on file[36]

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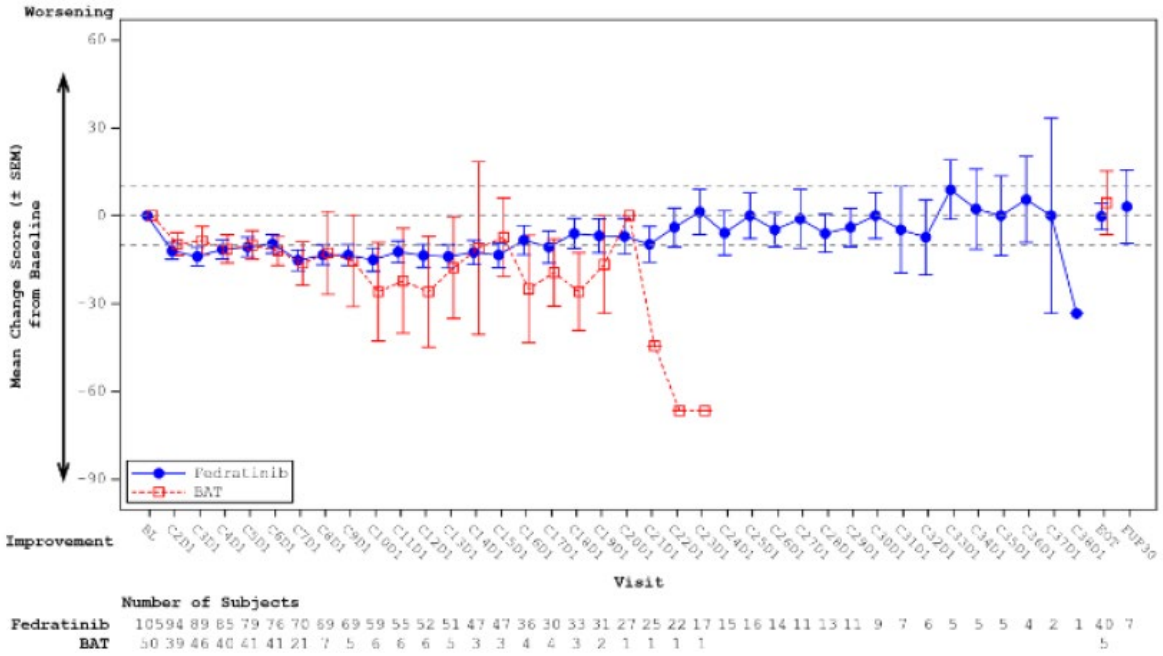
Fatigue

In both treatment groups, there were decreases from baseline in the mean scores for fatigue, indicating improvement, during the treatment period through C6D1. Clinically meaningful change was observed at C2D1 through C5D1 for the fedratinib group and at C4D1 through C6D1 for the BAT group. At C6D1, the mean (SEM) change from baseline was −9.6 (28.07) for the fedratinib group and −11.1 (32.53) for the BAT group (Figure 17). Clinically meaningful HRQOL response by cycle results were supportive of these findings with clinically meaningful improvement being demonstrated for more participants than either no change or worsening in both groups at many timepoints.[36]

Figure 17. FREEDOM-2: EORTC QLQ-C30 Fatigue scores (HRQOL evaluable population)



BAT = best available therapy; BL = baseline; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Quality of Life of Cancer Patients (Core); EOT = end of treatment; HRQOL = health-related quality of life; MID = minimally important difference; SEM = standard error of mean.

Note: Horizontal reference lines indicated MID, considered a change of ± 10 points from baseline.

Source: BMS data on file[36]

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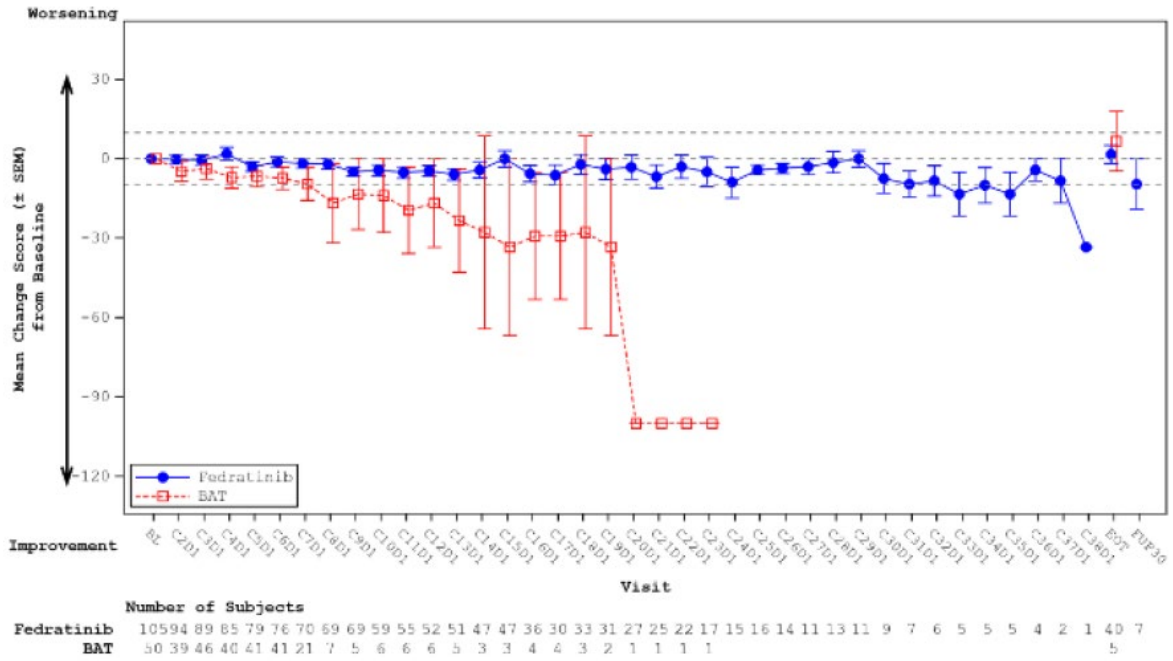
Nausea and vomiting

In both treatment groups, there were mostly decreases from baseline in the mean scores for nausea and vomiting, indicating improvement, in both treatment groups during the treatment period through C6D1. However, neither group showed clinically meaningful change at any timepoint. At C6D1, the mean (SEM) change from baseline was −1.1 (16.18) for the fedratinib group and −7.3 (26.89) for the BAT group (Figure 18). Clinically meaningful HRQOL response by cycle results were supportive of these findings, with most participants in both groups demonstrating no change at all timepoints.[36]

Figure 18. FREEDOM-2: EORTC QLQ-C30 Nausea and Vomiting scores (HRQOL evaluable population)



BAT = best available therapy; BL = baseline; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Quality of Life of Cancer Patients (Core); EOT = end of treatment; HRQOL = health-related quality of life; MID = minimally important difference; SEM = standard error of mean.

Note: Horizontal reference lines indicated MID, considered a change of ± 10 points from baseline.

Source: BMS data on file[36]

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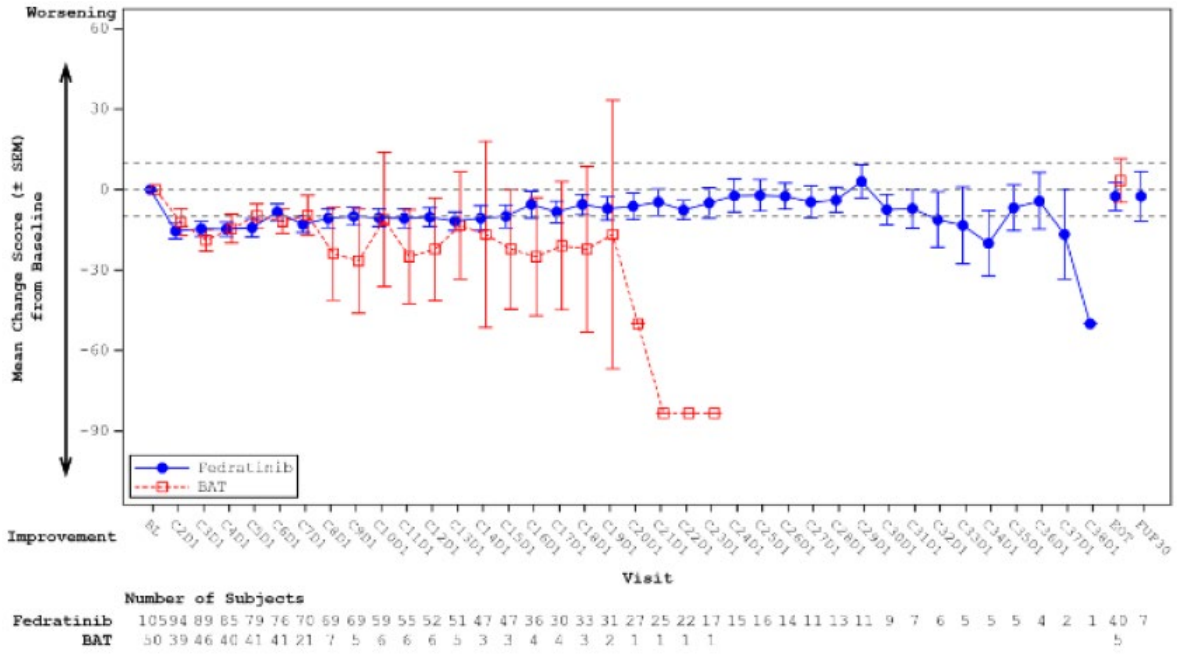
Pain

In both treatment groups, there were decreases from baseline in the mean scores for pain, indicating improvement, during the treatment period through C6D1. Clinically meaningful change emerged at C2D1 through C5D1 for the fedratinib group and at C2D1 through C4D1 and C6D1 for the BAT group. At C6D1, the mean (SEM) change from baseline was −8.3 (27.15) for the fedratinib group and −11.8 (28.93) for the BAT group (Figure 19). Clinically meaningful HRQOL response by cycle results were supportive of these findings with clinically meaningful improvement being demonstrated in more participants than either no change or worsening in both groups at many timepoints.[36]

Figure 19. FREEDOM-2: EORTC QLQ-C30 Pain scores (HRQOL evaluable population)



BAT = best available therapy; BL = baseline; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Quality of Life of Cancer Patients (Core); EOT = end of treatment; HRQOL = health-related quality of life; MID = minimally important difference; SEM = standard error of mean.

Note: Horizontal reference lines indicated MID, considered a change of ± 10 points from baseline.

Source: BMS data on file[36]

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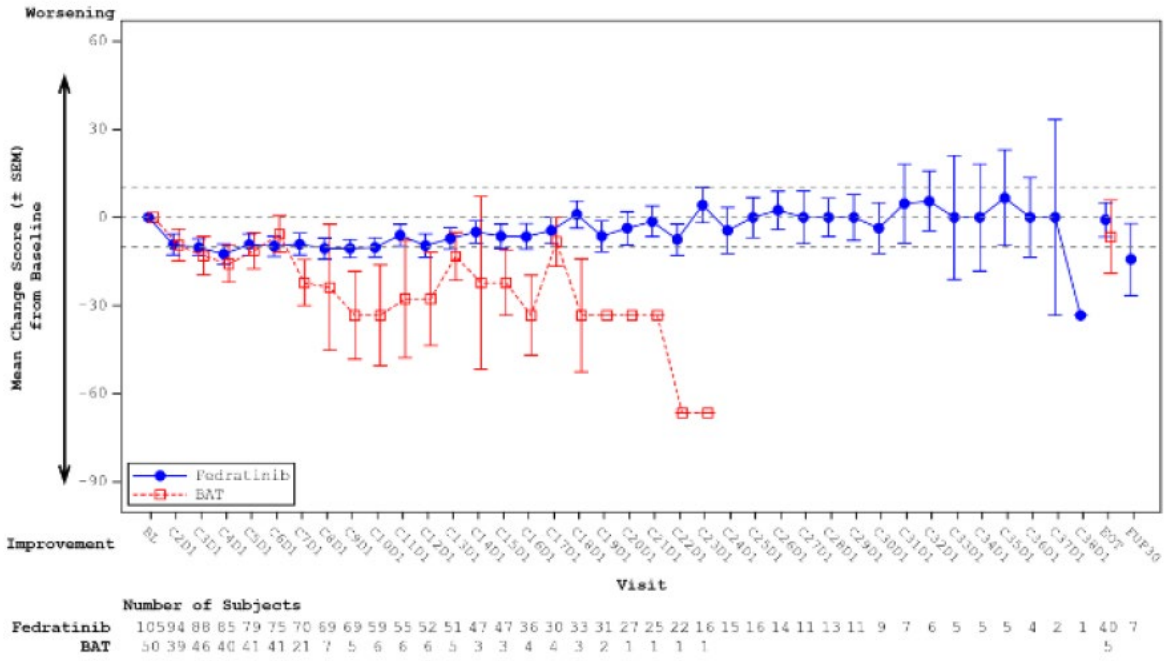
Dyspnoea

In both treatment groups, there were decreases from baseline in the mean scores for dyspnoea, indicating improvement, during the treatment period through C6D1. Clinically meaningful change was observed at C3D1 and C4D1 for the fedratinib group and at C3D1 through C5D1 for the BAT group. At C6D1, the mean (SEM) change from baseline was −9.8 (29.90) for the fedratinib group and −5.7 (39.37) for the BAT group (Figure 20). Clinically meaningful HRQOL response by cycle results were supportive of these findings, with most participants demonstrating clinically meaningful improvement or no change in both groups at all timepoints.[36]

Figure 20. FREEDOM-2: EORTC QLQ-C30 Dyspnoea scores (HRQOL evaluable population)



BAT = best available therapy; BL = baseline; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Quality of Life of Cancer Patients (Core); EOT = end of treatment; HRQOL = health-related quality of life; MID = minimally important difference; SEM = standard error of mean.

Note: Horizontal reference lines indicated MID, considered a change of ± 10 points from baseline.

Source: BMS data on file[36]

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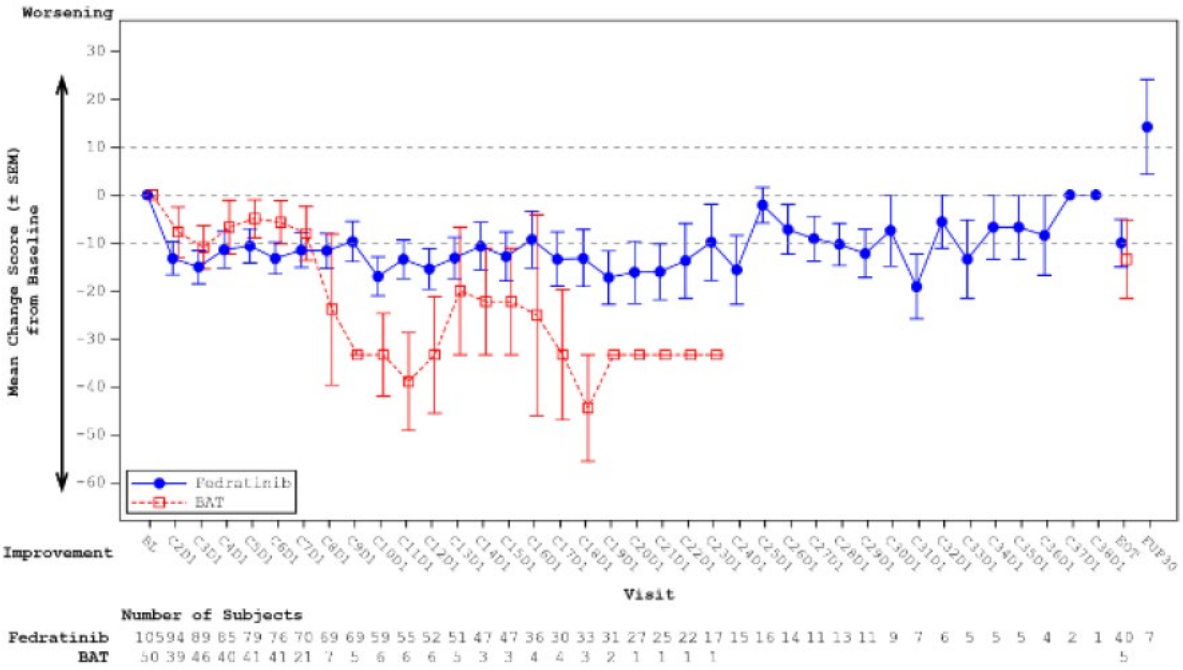
Insomnia

In both treatment groups, there were decreases from baseline in the mean scores for insomnia, indicating improvement, during the treatment period through C6D1. Clinically meaningful change was observed at all timepoints for the fedratinib group and at C3D1 for the BAT group. At C6D1, the mean (SEM) change from baseline was −13.2 (28.84) for the fedratinib group and −5.7 (28.77) for the BAT group (Figure 21). Clinically meaningful HRQOL response by cycle results were supportive of these findings, with most participants demonstrating clinically meaningful improvement or no change in both groups at all timepoints.[36]

Figure 21. FREEDOM-2: EORTC QLQ-C30 Insomnia scores (HRQOL evaluable population)



BAT = best available therapy; BL = baseline; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Quality of Life of Cancer Patients (Core); EOT = end of treatment; HRQOL = health-related quality of life; MID = minimally important difference; SEM = standard error of mean.

Note: Horizontal reference lines indicated MID, considered a change of ± 10 points from baseline.

Source: BMS data on file[36]

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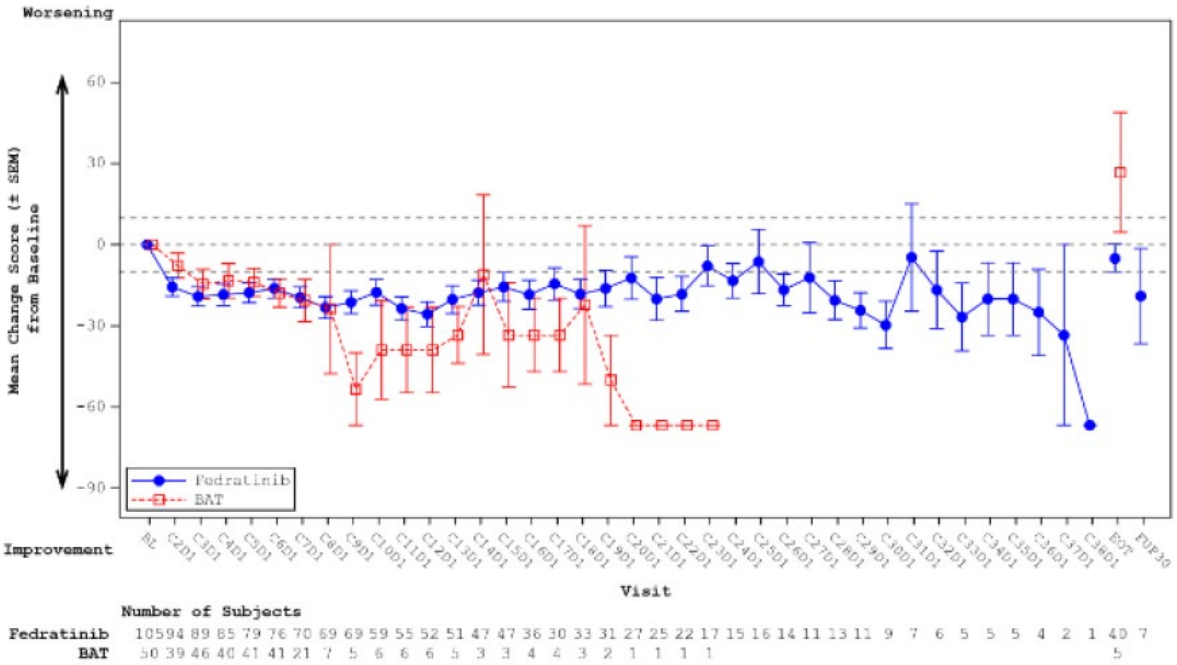
Appetite loss

In both treatment groups, there were decreases from baseline in the mean scores for appetite loss, indicating improvement, during the treatment period through C6D1. Clinically meaningful change was observed at all timepoints for the fedratinib group and at C3D1 through C6D1 for the BAT group. At C6D1, the mean (SEM) change from baseline was −16.2 (30.55) for the fedratinib group and −17.9 (33.41) for the BAT group (Figure 22). Clinically meaningful HRQOL response by cycle results were supportive of these findings with most participants demonstrating clinically meaningful improvement or no change in both groups at all timepoints.[36]

Figure 22. FREEDOM-2: EORTC QLQ-C30 Appetite Loss scores (HRQOL evaluable population)



BAT = best available therapy; BL = baseline; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Quality of Life of Cancer Patients (Core); EOT = end of treatment; HRQOL = health-related quality of life; MID = minimally important difference; SEM = standard error of mean.

Note: Horizontal reference lines indicated MID, considered a change of ± 10 points from baseline.

Source: BMS data on file[36]

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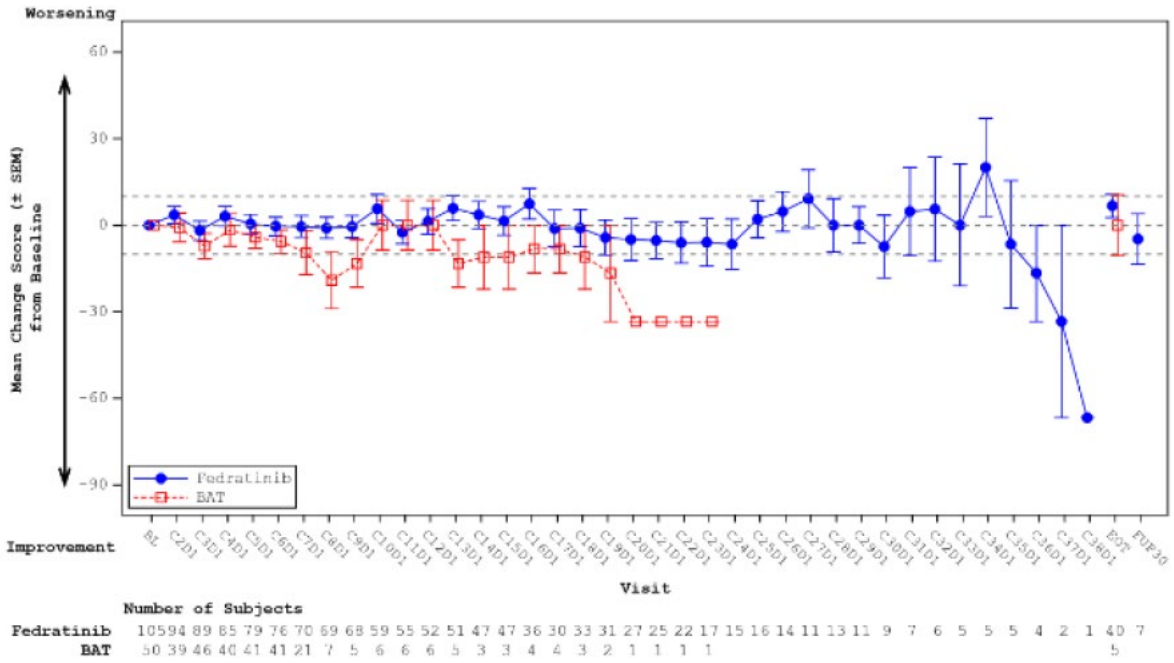
Constipation

In the BAT group, there were mostly decreases from baseline in the mean scores for constipation, indicating improvement, during the treatment period through C6D1 whereas the fedratinib group showed little change. However, neither group showed clinically meaningful change at any timepoint. At C6D1, the mean (SEM) change from baseline was −0.4 (27.48) for the fedratinib group and −5.7 (25.71) for the BAT group (Figure 23). Clinically meaningful HRQOL response by cycle results were supportive of these findings with most participants in both groups demonstrating no change at all timepoints.[36]

Figure 23. FREEDOM-2: EORTC QLQ-C30 Constipation scores (HRQOL evaluable population)



BAT = best available therapy; BL = baseline; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Quality of Life of Cancer Patients (Core); EOT = end of treatment; HRQOL = health-related quality of life; MID = minimally important difference; SEM = standard error of mean.

Note: Horizontal reference lines indicated MID, considered a change of ± 10 points from baseline.

Source: BMS data on file[36]

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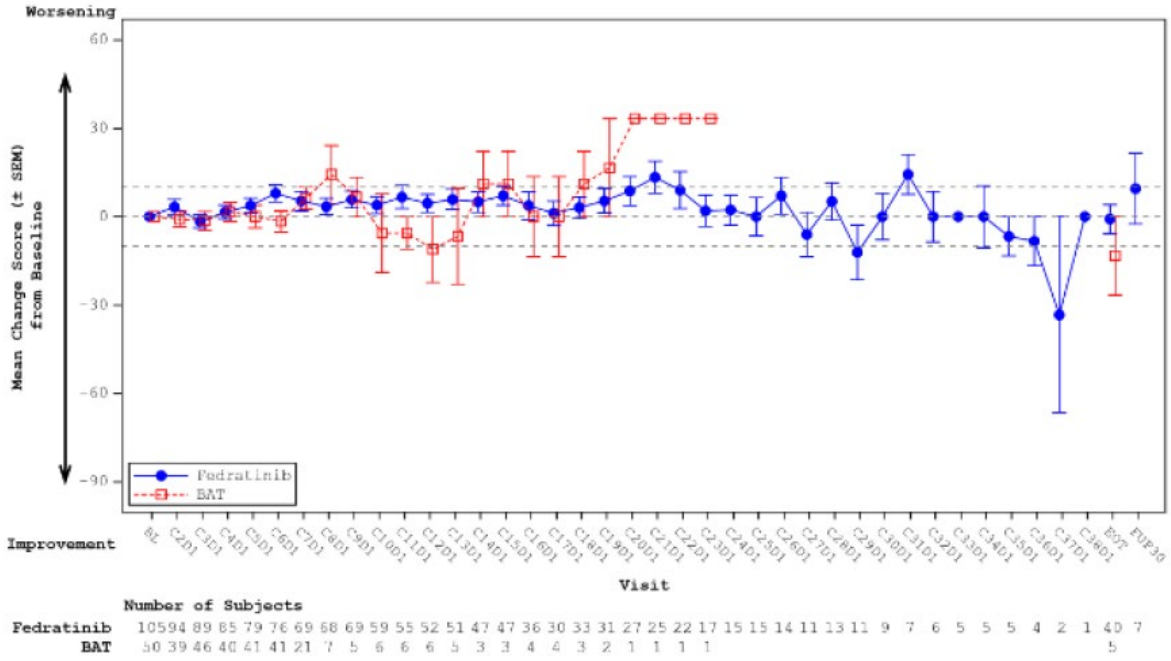
Diarrhoea

In both treatment groups, there were both small increases, indicating deterioration, and decreases, indicating improvement, from baseline in the mean scores for diarrhoea at various point during the treatment period through C6D1. However, neither group showed clinically meaningful change at any timepoint. At C6D1, the mean (SEM) change from baseline was 7.9 (24.87) for the fedratinib group and −1.6 (23.51) for the BAT group (Figure 24). Clinically meaningful HRQOL response results by cycle were supportive of these findings, with no change emerging for most of participants in both groups at all timepoints.[36]

Figure 24. FREEDOM-2: EORTC QLQ-C30 Diarrhoea scores (HRQOL evaluable population)



BAT = best available therapy; BL = baseline; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Quality of Life of Cancer Patients (Core); EOT = end of treatment; HRQOL = health-related quality of life; MID = minimally important difference; SEM = standard error of mean.

Note: Horizontal reference lines indicated MID, considered a change of ± 10 points from baseline.

Source: BMS data on file[36]

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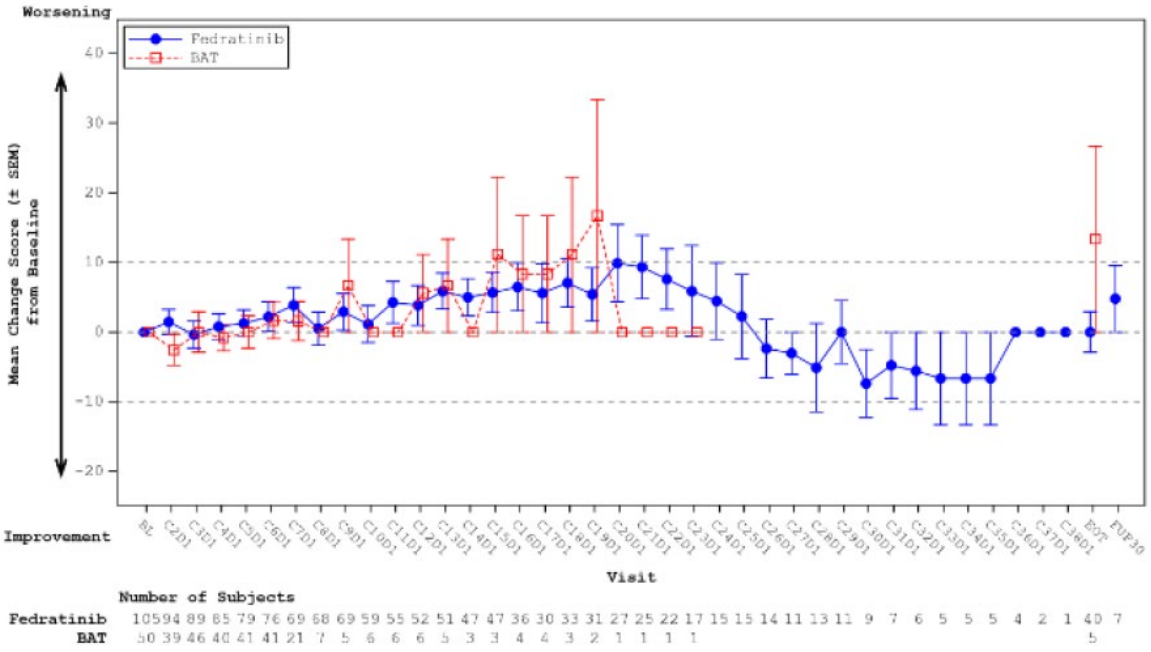
Financial difficulties

In both treatment groups, there were both small increases, indicating deterioration, and decreases, indicating improvement, from baseline in the mean scores for financial difficulties at various points during the treatment period through C6D1. Neither group showed clinically meaningful change at any timepoint. At C6D1, the mean (SEM) change from baseline was 2.2 (18.33) for the fedratinib group and 1.6 (16.59) for the BAT group (Figure 25). Clinically meaningful HRQOL response results by cycle were supportive of these findings, with no change being demonstrated for most participants in both groups at all timepoints.[36]

Figure 25. FREEDOM-2: EORTC QLQ-C30 Financial Difficulties scores (HRQOL evaluable population)



BAT = best available therapy; BL = baseline; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Quality of Life of Cancer Patients (Core); EOT = end of treatment; HRQOL = health-related quality of life; MID = minimally important difference; SEM = standard error of mean.

Note: Horizontal reference lines indicated MID, considered a change of ± 10 points from baseline.

Source: BMS data on file[36]

EQ-5D-5L

At baseline, the completion of the EQ-5D-5L as reflected in the adherence rate was 100.0% in both treatment groups. At C6D1, the adherence rate was 90.4% in the fedratinib group and 87.5% in the BAT group. The completion rates declined more quickly due to inclusion of participants discontinuing from the study, with 72.8% in the fedratinib group and 80.8% in the BAT group. No remarkable differences in the baseline scores between the treatment groups were noted for the EQ-5D-5L visual analogue score and Utility Score. Results are summarised for timepoints up to EOC6 due to potential crossover of participants in the BAT group to fedratinib afterwards. For the visual analogue score, both treatment groups had increases from baseline in the mean scores, indicating improvement, during the treatment period through C6D1. The fedratinib group showed clinically meaningful change at C2D1 through C5D1. The BAT group had no timepoints with clinically meaningful change. At C6D1, the mean (SEM) change from baseline was 6.2 (18.97) for the fedratinib group and 3.5 (23.29) for the BAT group (Figure 26).[36]

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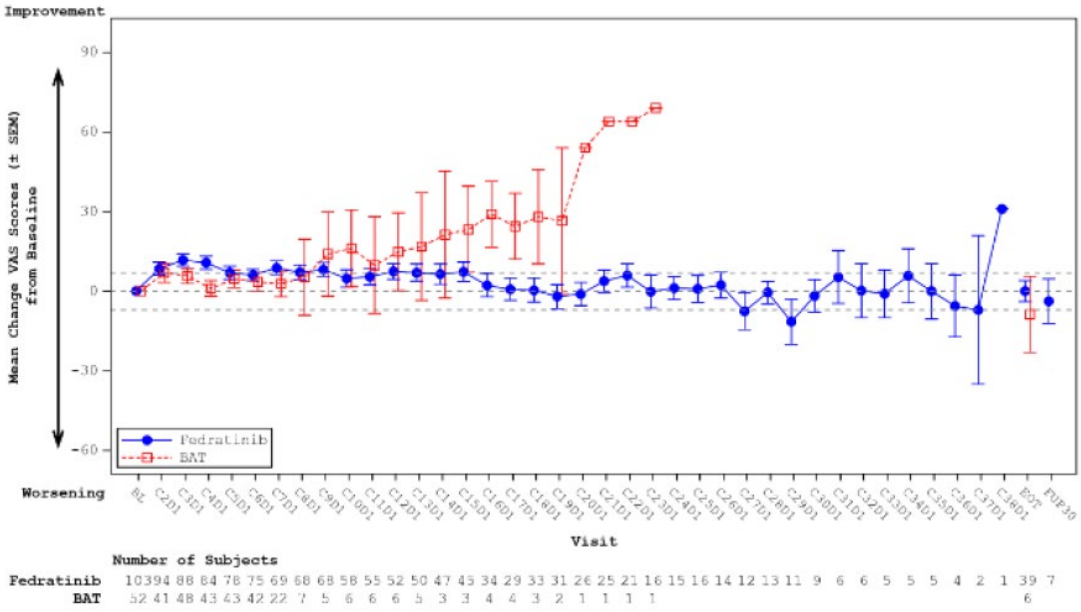
Figure 26. FREEDOM-2: EQ-5D-5L visual analogue scale, mean change from baseline (HRQOL evaluable population)

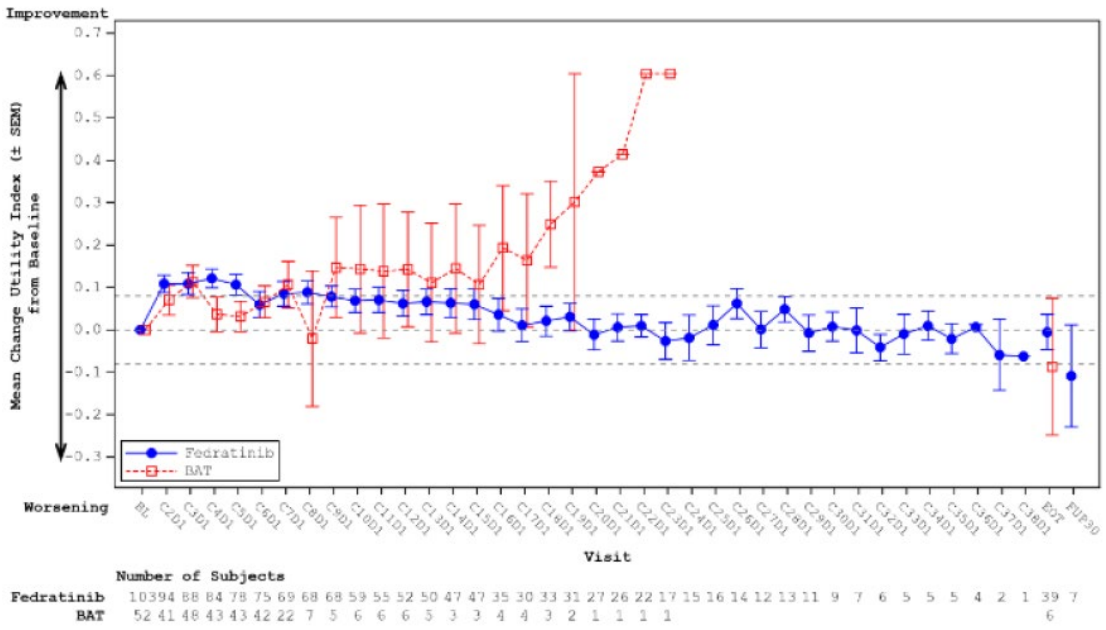


BAT = best available therapy; BL = baseline; EOT = end of treatment; HRQOL = health-related quality of life; SEM = standard error of mean; VAS = visual analogue score.

Source: BMS data on file[36]

In both treatment groups, there were increases from baseline in the mean scores for the Utility Score, indicating improvement, during the treatment period through C6D1. The fedratinib group showed clinically meaningful change at C2D1 through C5D1, and the BAT group showed clinically meaningful change at C3D1. At C6D1, the mean (SEM) change from baseline was 0.0594 (0.26864) for the fedratinib group and 0.0658 (0.24229) for the BAT group (Figure 27).[36]

Figure 27. FREEDOM-2: EQ-5D-5L utility index, mean change from baseline (HRQOL evaluable population)



BAT = best available therapy; BL = baseline; EOT = end of treatment; HRQOL = health-related quality of life; SEM = standard error of mean.

Source: BMS data on file[36]

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B.2.6.1.5 Exploratory efficacy outcomes

Time to spleen response by palpation

The median time to spleen response by palpation was 20.3 weeks (95% CI, 12.6-45.9) in the fedratinib group and NE in the BAT group. These results were based on data of 71 participants (53.0%) in the fedratinib group and 11 (16.9%) in the BAT group. In 2 participants in the BAT group, the spleen size was less than 5 cm below at baseline, so that their data were not included in this calculation.[36]

Best spleen volume response

The proportion of participants with best spleen volume response rate during the first 6 treatment cycles (BRR6) of ≥ 35% SVR as well as the proportion of participants with best spleen volume response rate during the full treatment period (BRR) of ≥ 35% SVR was higher in the fedratinib group than in the BAT group (Table 20).[36]

Table 20. FREEDOM-2: BRR6 and BRR by MRI/CT scan (ITT population)

Response	Fedratinib (N = 134)	BAT (N = 67)
Participants with ≥ 35% reduction in spleen volume within the first 6 treatment cycles (BRR6), n (%); (95% CI)[a]	66 (49.3); (40.5-58.0)	8 (11.9); (5.3-22.2)
Stratified analysis, based on eCRF[b] Difference in proportion (95% CI)[c]; *P* value	37.0 (25.6-48.3); < 0.0001	
Participants with ≥ 35% reduction in spleen volume during full treatment period (BRR), n (%); (95% CI)[b]	72 (53.7); (44.9-62.4)	8 (11.9); (5.3-22.2)
Stratified analysis, based on eCRF[c] Difference in proportion (95% CI); *P* value	41.3 (30.0-52.6); < 0.0001	

BAT = best available therapy; BRR = best spleen volume response rate during full treatment; BRR6 = best spleen volume response rate during the first 6 treatment cycles; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; CT = computed tomography; eCRF = electronic case report form; ITT = intention to treat; MRI = magnetic resonance imaging.

[a] The 2-sided 95% CI was based on the exact Clopper-Pearson method.

[b] The stratified *P* value was one-sided based on CMH test using the Greenland and Robins method to adjust for stratification factors: spleen size by palpation and platelet counts. The third stratification factor 'refractory/relapsed or intolerance to ruxolitinib treatment' was dropped due to small cell count issue.

[c] The 95% CI of the difference was based on Greenland and Robins method.

Source: BMS data on file[36]

Anaemia response

Anaemia response was found in 20 participants (19.8%) in the fedratinib group and 12 (22.6%) in the BAT group.[36]

B.2.6.1.6 FREEDOM-2: overall survival crossover adjustment

A total of 68.7% of participants crossed over from BAT to fedratinib during FREEDOM-2. In an ITT analysis, the outcomes were analysed according to the intervention a participant was randomly assigned to, regardless of treatment switching. Patient crossover affects the OS analysis (for the ITT analysis), specifically the relative treatment effects, because outcomes in the control arm may be influenced by both the control and experimental treatment after crossover. In cases in which the experimental treatment is more effective than the control, this will result in an underestimation of the

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true relative treatment effect of the experimental treatment. This can lead to some complex uncertainty. Therefore, crossover adjustment was performed.

A literature review was conducted to identify alternative crossover-adjustment methods. Five alternative OS crossover-adjustment methods were identified, including randomisation-based methods to estimate counterfactual survival (rank-preserving structure failure time [RPSFT] and iterative parameter estimation [IPE]), the 2-stage methods (simplified 2-stage estimation [TSEsimp] and complex 2-stage estimation with g-estimation [TSEgest]), and the propensity-based method (inverse probability of censoring weighting [IPCW]).

Three methodologies were applied for FREEDOM-2 to account for treatment switching from BAT to fedratinib: RPSFT, TSEsimp, and IPCW. Additional approaches (i.e., IPE and TSEgest) were not considered due to challenges with respect to the methods explored. The IPE method assumes that the only difference between randomly assigned groups is the treatment received and a common treatment effect and that the survival times follow a parametric distribution; as such, the IPE method was deemed unsuitable. TSEgest requires a strong assumption of no unmeasured confounding over time and, as such, was deemed unsuitable.[51]

Rank-preserving structure failure time (RPSFT) model

In the RPSFT model, the crossover-adjusted estimates improved the OS for BAT when predicting the counterfactuals had participants in BAT not crossed over to receive fedratinib. This finding was not consistent with the choice of clinicians to switch participants to fedratinib (69% crossed over) and therefore lacks face validity. Additionally, the simplified 2-stage-adjusted results were biased due to the acceleration factors lacking face validity. Finally, the short-term follow-up available in participants in BAT who did not cross over is a major limitation of the IPCW approach. The IPCW-adjusted BAT curve was closely aligned with the naive approach of censoring participants at crossover, suggesting that the weights had a minimal impact to account for informative censoring.[51] The contradictory results and the likely violation of the crossover-adjustment methods are the reasons why none of the estimates from the explored methods are recommended. As such, estimates obtained from the crossover-adjustment methods are not considered reliable in this context.[51] However, the results are presented for transparency.

A KM overlay of OS stratified by crossover status for the BAT arm is presented in Figure 28. Out of the 67 participants randomly assigned to receive BAT, 46 participants (69%) crossed over from BAT to fedratinib. Therefore, there were only 21 participants in BAT arm who did not cross over. Among the participants who crossed over, 43 (93%) did so after 6 cycles whereas the remaining 3 (7%) crossed over after progression, and the average time of treatment switch was 6.8 months (median, 6.3 months; range, 5.5-17.5).[51]

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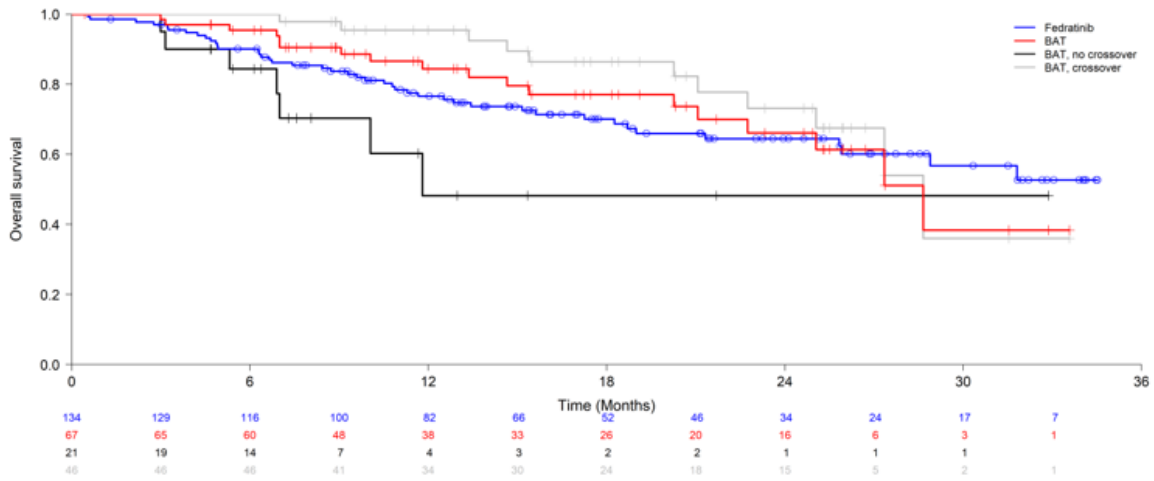
Figure 28. FREEDOM-2: Kaplan-Meier overlay of overall survival for ITT populations (fedratinib and BAT arms), stratified by crossover status

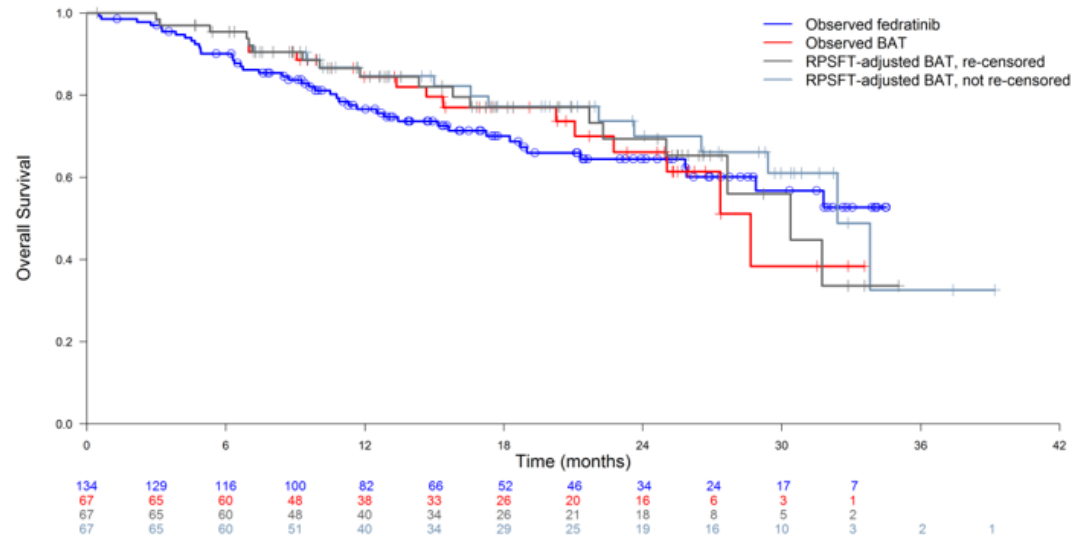


BAT = best available therapy.

Source: BMS data on file[51]

RPSFT-adjusted KM OS curves are presented in Figure 29. Typically, the observed OS estimates favour the new intervention versus the control arm, in which case the treatment effect estimated from the experimental arm and applied to the control arm results in OS predictions less favourable than observed estimates (i.e., are shrunken by acceleration factor) to reflect the hypothetical situation where participants in the control arm did not cross over. However, for FREEDOM-2, given that BAT has more favourable OS than fedratinib, the crossover-adjusted estimates improve the OS for BAT when predicting the counterfactuals had participants in BAT not crossed over to receive fedratinib. This finding was not consistent with the choice of clinicians to switch participants to fedratinib (69% crossed over) and therefore lacks face validity.[51]

Figure 29. FREEDOM-2: RPSFT-adjusted overall survival–adjusted Kaplan-Meier curves



BAT = best available therapy; RPSFT = rank-preserving structure failure time.

Source: BMS data on file[51]

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Simplified 2-stage estimation (TSEsimp)

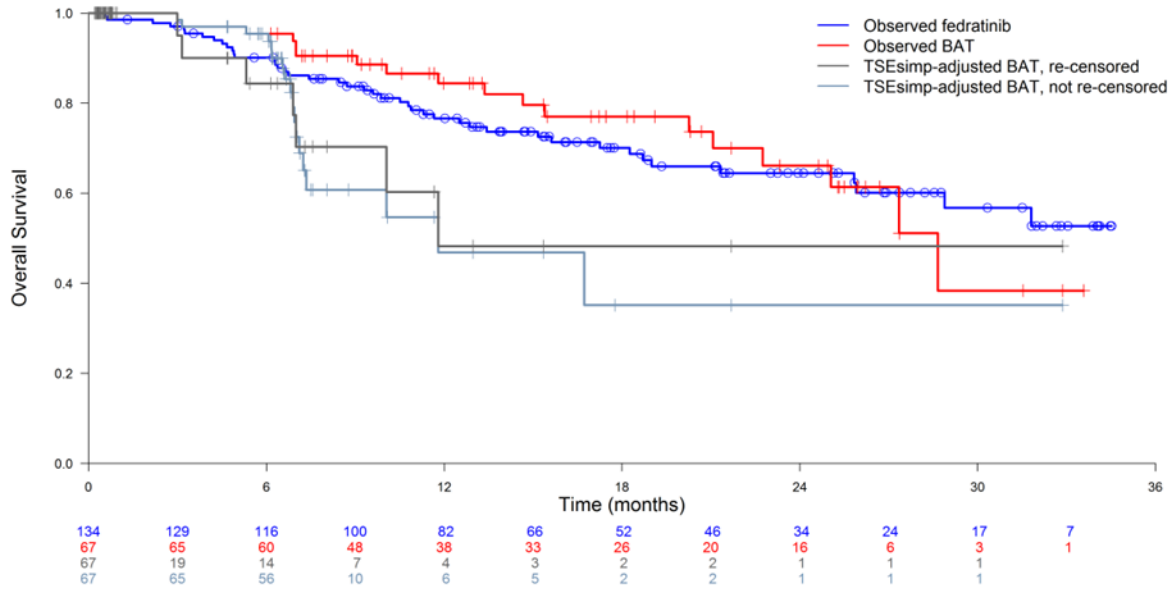
To estimate the effect of switching on survival, various models were tested (i.e., different accelerated failure time models), all of which resulted in an acceleration factor close to 0 (Table 21). This corresponds with a time ratio of 1:0, suggesting switchers have an infinitely longer survival time. Because we are unable to adequately estimate an acceleration factor that has any face validity, the TSEsimp method is not recommended, and any results may be biased.

Table 21. FREEDOM-2: acceleration factor estimated from different accelerated failure time models

Model	Acceleration factor
Weibull	1.078×10^{-20}
Log-logistic	0.0039
Log-normal	1.5753×10^{-07}
Gamma	0.0286
Generalised gamma	1.5873×10^{-06}

The TSEsimp-adjusted KM OS curves are presented in Figure 30. Note that these should be considered biased results due to the acceleration factors lacking face validity. Applying a near-zero acceleration factor to the post-crossover survival time resulted in truncating survival time in participants who crossed over to the point of treatment switch, driving the observed drop in the TSEsimp-adjusted KM curve (blue grey line) at 6 months. The recensored BAT arm (dark grey line) has a cluster of censored participants within the first month, which is a function of the acceleration factor being near zero, and as such the later timepoint results were driven by relatively few participants.[51]

Figure 30. FREEDOM-2: TSEsimp-adjusted overall survival–adjusted Kaplan-Meier curves



BAT = best available therapy; TSEsimp = simplified 2-stage estimation.

Source: BMS data on file[51]

Inverse probability of censoring weighting (IPCW)

The distribution of weights estimated for the IPCW method was considered reasonable (median weight, 0.99; range, 0.46-2.19). However, the short-term follow-up available in participants in the BAT arm who

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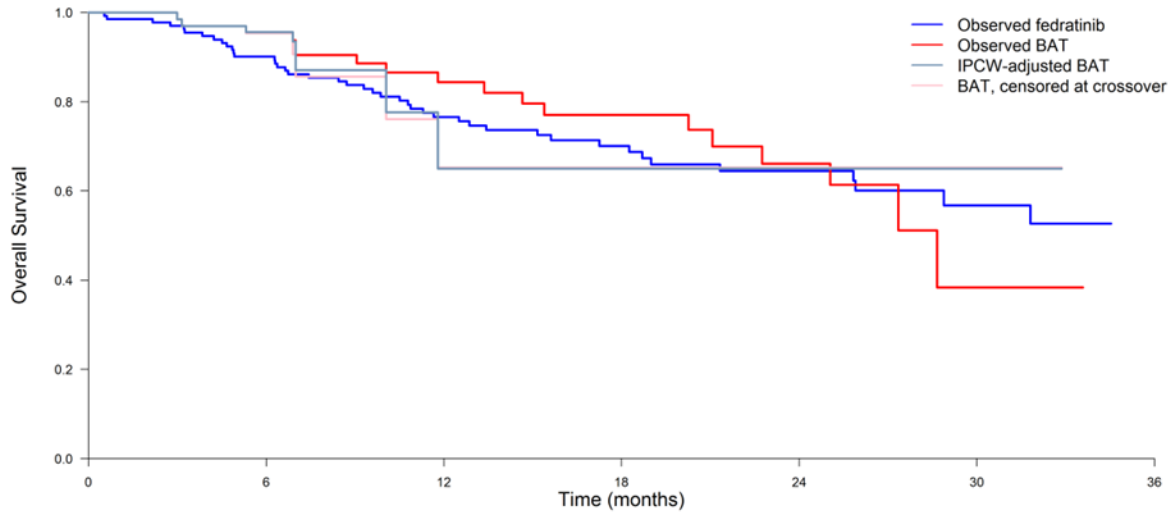
did not cross over (n = 21) is a major limitation of the IPCW approach. To implement the method, switchers were censored at time of crossover, and the remaining observations were weighted to account for bias introduced by censoring. However, most of the crossover happened around 6 months, at which point there were only 14 BAT participants who did not cross over who were remaining at risk of event. Therefore, any longer-term outcomes were driven by relatively few patients, which may introduce bias. Additionally, the lack of events (i.e., deaths) after 12 months suggests that any weighting performed would likely have minimal effect on long-term results because reweighting all censored participants cannot account for the curve flattening that occurs after 12 months. As such, the IPCW method is not recommended. Figure 31 presents the IPCW-adjusted KM OS curves. Of note, the IPCW-adjusted BAT curve was closely aligned with the naive approach of censoring participants at crossover, suggesting that the weights had minimal effect to account for informative censoring.[51]

Figure 31. FREEDOM-2: IPCW-adjusted overall survival–adjusted Kaplan-Meier curves



BAT = best available therapy; IPCW = inverse probability of censoring weighting.
Source: BMS data on file[51]

Figure 32 presents the IPCW-adjusted KM OS curves from a sensitivity analysis assuming that there was a zero probability of switching before cycle 6. When excluding observations before cycle 6 in the weight calculation, the IPCW-adjusted KM curve (dark grey line) shifted more than in the base-case analysis, but the results were still largely in line with the naive-censored approach (pink line). The weights remained reasonably distributed and concentrated around 1 (mean, 0.99; median, 1.00 [range, 0.43-3.25]).

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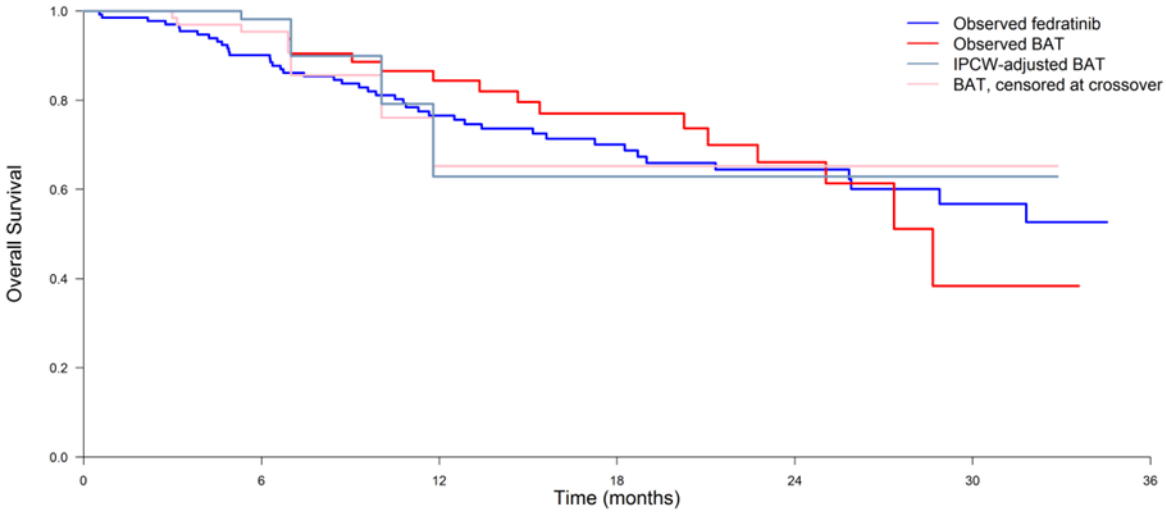
Figure 32. FREEDOM-2: IPCW-adjusted overall survival–adjusted Kaplan-Meier curves (sensitivity analysis assuming probability of switching before cycle 6 was zero)



BAT = best available therapy; IPCW = inverse probability of censoring weighting.

Conclusion of overall survival adjustment

When applied to FREEDOM-2, the RPSFT, TSEsimp, and IPCW methods all provided contradictory results. Of more importance, the underlying assumptions of the crossover-adjustment methods were likely violated. Overall, none of the estimates from the explored methods are recommended. Some of the trial characteristics of FREEDOM-2 contributed to the violations of the underlying assumptions of these methods. As such, estimates obtained from the crossover-adjustment methods are not considered reliable in this context, for instance, not having a universal cutoff applicable to all participants in order to accurately predict switching (in FREEDOM-2, crossover could occur either at postprogression [3 of 46 patients] or after cycle 6 [43 of 46 patients]). Also, the availability of data plays a crucial part, as a small sample size will limit the inclusion of feasible covariates. Because FREEDOM-2 was not powered for either OS or subgroup analysis, this results in an even lower sample size for the crossover analysis. Furthermore, a higher proportion of participants in the fedratinib arm received at least 1 prior systemic anticancer therapy (20.1%) compared with participants in the BAT arm (10.4%). Participants who received more than 4 prior anticancer therapies (5.2% in fedratinib, 0 in BAT) are presumably sicker compared with participants with less than 4 prior anticancer therapies. As such, OS estimates would favour the healthier population in the BAT arm.[51]

B.2.6.2 SACT data set

B.2.6.2.1 Primary outcome: treatment duration

Of the 54 patients included in the SACT data set analysis, 27 (50%) were classified as having completed treatment by 31 October 2022 (latest follow-up in SACT data set). Patients are assumed to have completed treatment if they have died, have an outcome summary recorded in the SACT data set, or they have not received treatment with fedratinib in at least 3 months. The median follow-up time in the SACT data set was 4.6 months (140 days). The median follow-up time in the SACT data set was the patients' median observed time from the start of their treatment to their last treatment date in SACT plus the prescription length. Due to differences in data submission procedures, the maximum follow-up period was either 11 months (applied to 94% of patients, n = 132) or 12 months (applied to 6%, n = 9).[46] Table 22 presents treatment status, and Table 23 presents treatment duration.

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Table 22. SACT data set: treatment status

Patient status	Frequency (N)	Percentage (%)
Patient died, not on treatment	12	22%
Patient died, on treatment	7	13%
Treatment stopped	8	15%
Treatment ongoing	27	50%
Total	54	100%

SACT = Systemic Anti-Cancer Therapy.

Source: NHS England data on file[46]

Table 23. SACT data set: treatment duration at 6- and 12-month intervals

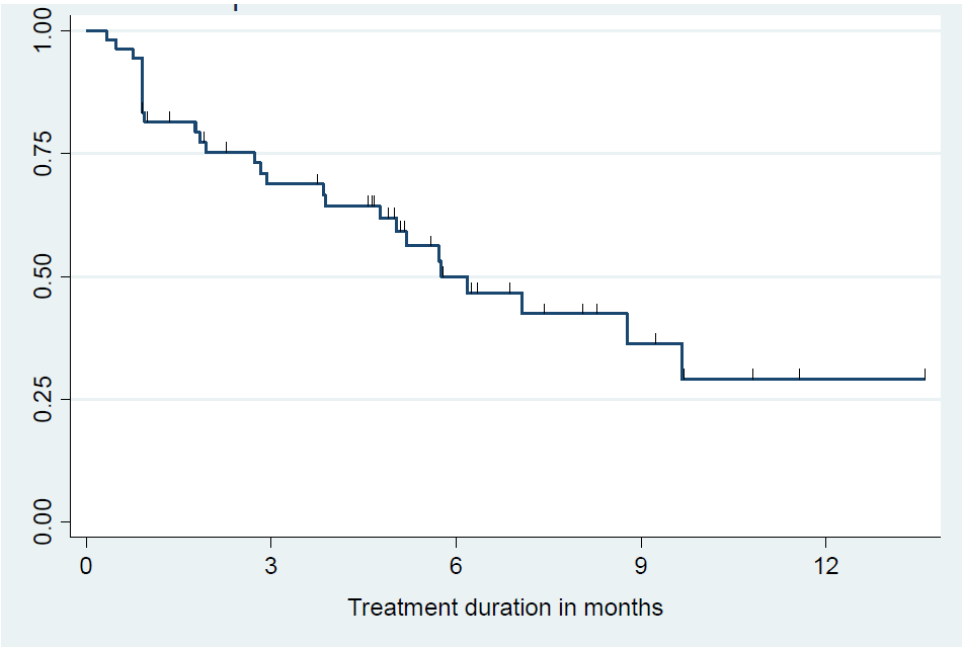
Time period	Treatment duration (%)
6 months	50% (95% CI, 34%-64%)
12 months	29% (95% CI, 13%-48%)

CI = confidence interval; SACT = Systemic Anti-Cancer Therapy.

Source: NHS England data on file[46]

Figure 33 presents the treatment duration estimate as a KM curve. The median treatment duration for all patients was 5.7 months (95% CI, 3.9-9.7 months) (173 days).[46]

Figure 33. SACT data set: Kaplan-Meier treatment duration (n = 54)



SACT = Systemic Anti-Cancer Therapy.

Source: NHS England data on file[46]

Table 24 presents the outcomes recorded for patients who ended treatment.[46]

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Table 24. SACT data set: treatment outcomes for patients who have ended treatment (n = 27)

Outcome	Frequency (N)	Percentage (%)
Stopped treatment, acute toxicity	7	26%
Stopped treatment, died on treatment	7	26%
Stopped treatment, progression of disease	6	22%
Stopped treatment, died not on treatment	5	19%
Stopped treatment, patient choice	2	7%
Total	27	100%

SACT = Systemic Anti-Cancer Therapy.

Source: NHS England data on file[46]

B.2.6.2.2 Primary outcome: overall survival

Of the 54 patients included in the initial SACT data set analysis, the minimum follow-up was 3.4 months (103 days) from the last CDF application. Patients were traced for their vital status on 13 February 2023. This date was used as the follow-up date (censored date) if a patient was still alive. The median follow-up time in the SACT data set was 7.5 months (228 days). Median follow-up was the patient's median observed time from the start of their treatment to death or censored date. A reassessment of vital status was performed on 5 February 2024; the median follow-up time was then 15.5 months (471 days).[46] Table 25 presents OS at 6, 12, 18, and 24 months.

Table 25. SACT data set: overall survival at 6-, 12-, 18-, and 24-month intervals

Time period	Overall survival (%)
6 months	74 (95 CI, 59-83)
12 months	57 (95 CI, 40-71)
18 months	42 (95 CI, 29-55)
24 months	36 (95 CI, 23-50)

CI = confidence interval; SACT = Systemic Anti-Cancer Therapy.

Source: NHS England data on file[46]

Figure 34 presents the OS estimate as a KM curve, censored on 5 February 2024. The median OS was 15.4 months (468 days).[46]

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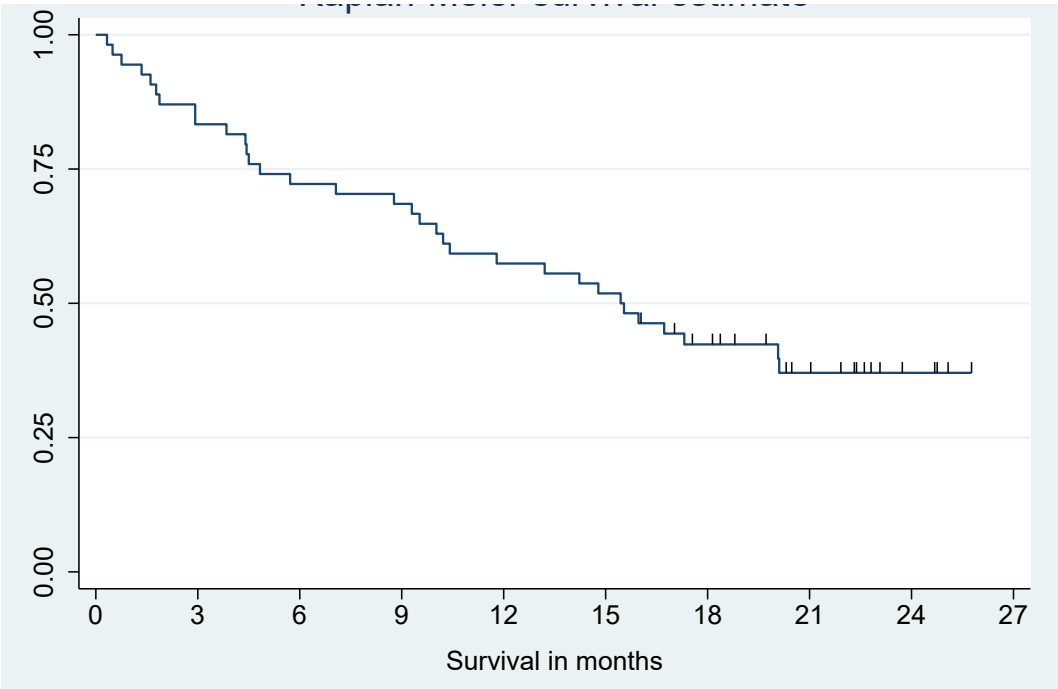
Figure 34. SACT data set: Kaplan-Meier survival plot (n = 54)



SACT = Systemic Anti-Cancer Therapy.

Source: NHS England data on file[46]

B.2.7 Subgroup analysis

B.2.7.1 FREEDOM-2

Subgroup analyses were carried out on the primary outcome (spleen response rate, ≥ 35% SVR at EOC6) to determine the treatment effect of fedratinib on clinically important subpopulations. Subpopulations were by baseline demographic and disease characteristics, platelet and haemoglobin count, and Eastern Cooperative Oncology Group (ECOG) performance status (PS).[36]

The treatment effect was consistent across subgroups (Figure 35), where fedratinib showed clinical benefit on spleen response rate, supporting the robustness of the results of the primary analysis. A possibly larger treatment effect was observed in the subgroup with platelet counts of 50 to < 100 × 10^9/L and the subgroup with ruxolitinib intolerance.[36]

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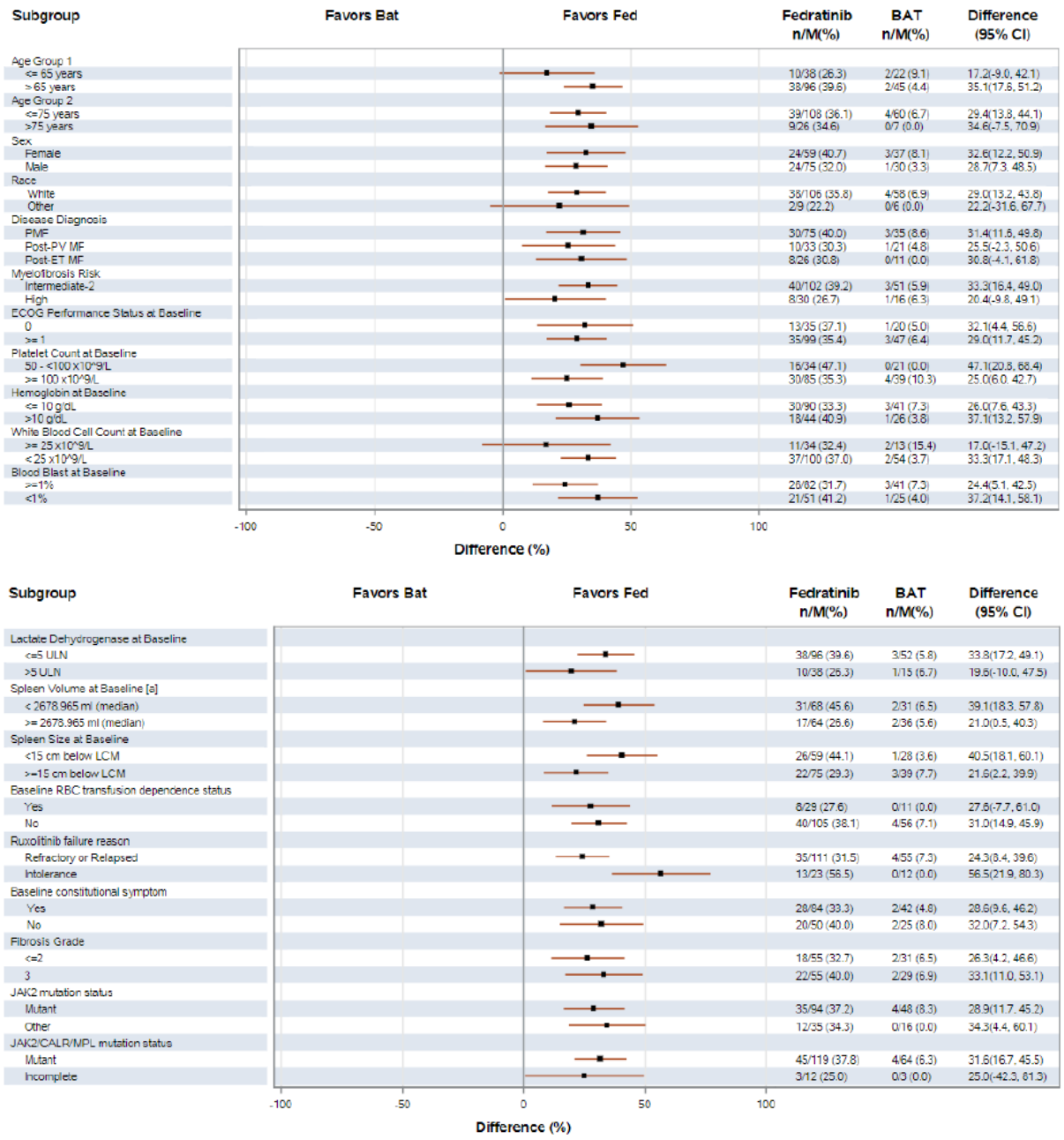
Figure 35. FREEDOM-2: ≥ 35% SVR at EOC6, forest plot (ITT population)



BAT = best available therapy; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; EOC6 = end of cycle 6; ITT = intention to treat; JAK2 = Janus kinase 2; LCM = left costal margin; PMF = primary myelofibrosis; post-ET MF = post-essential thrombocythemia myelofibrosis; post-PV MF = post-polycythemia vera myelofibrosis; RBC = red blood cell; SVR = spleen volume reduction; ULN = upper limit of normal.

Source: BMS data on file[36]

B.2.8 Meta-analysis

B.2.8.1 FREEDOM-2

As a single study with a head-to-head comparison of BAT, data for fedratinib are provided for patients treated with ruxolitinib. Therefore, meta-analysis of intervention studies is not required.

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B.2.9 Indirect and mixed treatment comparisons

B.2.9.1 FREEDOM-2

Because FREEDOM-2 is a head-to-head study including a comparison with BAT, no indirect comparisons or mixed treatment comparisons are included in this submission for FREEDOM-2.

B.2.10 Adverse reactions

B.2.10.1 Treatment exposure

B.2.10.1.1 FREEDOM-2

The median number of treatment cycles was 11 (range, 1.0-38) in the fedratinib all-treated arm, 10 (range, 1-26) in the crossover arm, and 7 (range, 1-23) in the BAT arm. The mean duration of treatment exposure was 52.5 weeks (standard deviation [SD], 39.68) in the all-treated fedratinib arm, 41.7 weeks (SD, 29.95) in the crossover arm, and 27.7 weeks (SD, 15.29) in the BAT arm. Treatment discontinuation in the fedratinib arm before the completion of 6 cycles was most frequently due to AEs in 10 participants (7.5%), followed by the decision of the physician in 7 participants (5.2%). In the BAT arm, the most frequent reasons for treatment discontinuation before the end of 6 cycles were AEs and participant decision, with each having 3 participants (4.5%).[36] In the fedratinib all-treated and crossover population, approximately 50% of participants completed 12 cycles, and only 10% in the BAT arm completed 12 cycles. Relative dose intensity (RDI) was 86.9% and 90.5% in all-treated and crossover fedratinib arms, respectively, suggesting overall tolerability. Table 26 summarises treatment exposure in FREEDOM-2.

Table 26. FREEDOM-2: fedratinib exposure (all-treated population and crossover population)

	All-treated		Crossover
	Fedratinib (n = 134)	**BAT (n = 67)**	**Fedratinib (n = 46)**
Cycles administered			
Mean (SD)	13.5 (9.65)	7.3 (3.63)	10.9 (7.30)
Median (min, max)	11.0 (1, 38)	7.0 (1, 23)	10.0 (1, 26)
Cycles completed, n (%)			
1 cycle	134 (100)	67 (100)	45 (97.8)
2 cycles	128 (95.5)	66 (98.5)	43 (93.5)
3 cycles	125 (93.3)	65 (97.0)	39 (84.8)
4 cycles	115 (85.8)	63 (94.0)	37 (80.4)
5 cycles	108 (80.6)	60 (89.6)	33 (71.7)
6 cycles	100 (74.6)	59 (88.1)	31 (67.4)
9 cycles	85 (63.4)	8 (11.9)	25 (54.3)
12 cycles	66 (49.3)	7 (10.4)	21 (45.7)
15 cycles	56 (41.8)	4 (6.0)	14 (30.4)
18 cycles	38 (28.4)	3 (4.5)	9 (19.6)
21 cycles	30 (22.4)	1 (1.5)	8 (17.4)
24 cycles	24 (17.9)	0	2 (4.3)

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	All-treated		Crossover
	Fedratinib (n = 134)	BAT (n = 67)	Fedratinib (n = 46)
Duration of exposure[a] (weeks)			
Mean (SD)	52.5 (39.68)	27.7 (15.29)	41.7 (29.95)
Median (min, max)	43 (1, 151)	24.7 (1, 97)	39.3 (0, 105)
Actual dose intensity[b] (mg/week)			
Mean (SD)	2,434 (473.24)	NA	2,533.8 (368.87)
Median (min, max)	2,708.1 (1,148, 2,800)	NA	2,747.7 (1,455, 2,800)
Relative dose intensity[c] (%)			
Mean (SD)	86.9 (16.9)	NA	90.5 (13.17)
Median (min, max)	96.7 (41, 100)	NA	98.1 (52, 100)
Cumulative dose, mg			
Mean (SD)	128,019.4 (98,123.08)	NA	106,217.8 (80,378.75)
Median (min, max)	113,600 (2,000, 416,000)	NA	93,200 (400, 257,500)

BAT = best available therapy; C1D1 = cycle 1, day 1; max = maximum; min = minimum; NA = not applicable; SD = standard deviation.

[a] Treatment duration = (last dose date – first dose date + 1) ÷ 7, regardless of unplanned intermittent discontinuations. For participants in BAT group, C1D1 is treated as first dose date. For last dose date (treatment end date), treatment discontinuation date is used if participant discontinues the study treatment without crossover; (crossover date-1) is used if participant crosses over to fedratinib group; for ongoing participants, data cutoff date is used.

[b] Actual dose intensity = cumulative dose ÷ treatment duration.

[c] Relative dose intensity = actual dose intensity ÷ planned dose Intensity (of 2,800 mg/week), presented as a percentage.

Source: BMS data on file[45]

B.2.10.2 Summary of safety data

In FREEDOM-2, treatment-emergent AEs (TEAEs) included any AEs with onset or worsening of grade between the date of first dose and 30 days after the date of last dose. At least 1 TEAE was experienced in more than 97% of the fedratinib all-treated and crossover populations and the BAT arm. Grade 3 or 4 TEAEs were reported in 76.9%, 67.4%, and 55.2% of participants in the fedratinib all-treated and crossover populations and BAT arm, respectively.[45] Table 27 presents an overview of the TEAEs associated with fedratinib in FREEDOM-2.

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Table 27. FREEDOM-2: safety overview (all-treated fedratinib, BAT, and crossover fedratinib populations)

No. of events[a] (%)	Fedratinib (n = 134)	BAT (n = 67)	Crossover fedratinib (n = 46)
TEAEs	132 (98.5)	65 (97.0)	46 (100)
Treatment-related TEAEs	116 (86.6)	24 (35.8)	44 (95.7)
Grade 3 or 4 TEAEs	103 (76.9)	37 (55.2)	31 (67.4)
Treatment-related grade 3 or 4 TEAEs	62 (46.3)	10 (14.9)	18 (39.1)
TEAE leading to death	21 (15.7)	4 (6.0)	4 (8.7)
Treatment-related TEAE leading to death	NR	NR	NR
Treatment-emergent SAEs	72 (53.7)	21 (31.3)	16 (34.8)
Treatment-related treatment-emergent SAEs	25 (18.7)	2 (3.0)	5 (10.9)
TEAEs leading to permanent treatment discontinuation	24 (17.9)	4 (6.0)	7 (15.2)
TEAEs leading to dose modification	NR	NR	NR
TEAEs leading to dose reduction	48 (35.8)	7 (10.4)	18 (39.1)
TEAEs leading to dose interruption	52 (38.8)	4 (6.0)	15 (32.6)

BAT = best available therapy; NR = not reported; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Note: For the fedratinib group, only data for participants who were initially treated with fedratinib are summarised. For crossover participants in the BAT arm, only data before crossover are included.

[a] No. of events refers to number of participants with at least 1 TEAE or 1 SAE.

Source: FREEDOM-2 CSR[45]

B.2.10.3 Common adverse event data

B.2.10.3.1 FREEDOM-2

The most common TEAEs by study arm were (number of participants [%])[45]:

- Fedratinib all-treated: diarrhoea (62 [46.3%]), anaemia (59 [44%]), nausea (54 [40.3%])
- Fedratinib crossover: anaemia (20 [43.5%]), diarrhoea (17 [37%]), thrombocytopenia (13 [28.3%])
- BAT all-treated: anaemia (24 [35.8%]), asthenia (16 [23.9%]), thrombocytopenia (12 [17.9%])

The most common treatment-related TEAEs by study arm were (number of participants [%])[45]:

- Fedratinib all-treated: diarrhoea (54 [40.3%]), nausea (45 [33.6%]), thrombocytopenia (32 [23.9%])
- Fedratinib crossover: diarrhoea (15 [32.6%]), anaemia (14 [30.4%]), nausea (11 [23.9%])
- BAT all-treated: anaemia (9 [13.4%]), thrombocytopenia (4 [6%]), constipation (3 [4.5%])

A summary of the common AEs reported in FREEDOM-2 is presented in Table 28 for fedratinib all-treated fedratinib and BAT populations and Table 29 for the fedratinib crossover population.

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Table 28. FREEDOM-2: common treatment-emergent and treatment-related adverse events (all-treated population)

	Treatment-emergent		Treatment-related	
	Fedratinib (n = 134)	BAT (n = 67)	Fedratinib (n = 134)	BAT (n = 67)
Participants with at least 1 TEAE	131 (97.8)	58 (86.6)	103 (76.9)	13 (19.4)
Anaemia	59 (44)	24 (35.8)	22 (16.4)	9 (13.4)
Thrombocytopenia	48 (35.8)	12 (17.9)	32 (23.9)	4 (6)
Leukocytosis	5 (3.7)	5 (7.5)	NR	NR
Diarrhoea	62 (46.3)	3 (4.5)	54 (40.3)	0
Nausea	54 (40.3)	10 (14.9)	45 (33.6)	1 (1.5)
Vomiting	25 (18.7)	3 (4.5)	19 (14.2)	1 (1.5)
Constipation	30 (22.4)	6 (9)	12 (9)	3 (4.5)
Asthenia	27 (20.1)	16 (23.9)	NR	NR
Oedema peripheral	26 (19.4)	7 (10.4)	NR	NR
COVID-19	21 (15.7)	7 (10.4)	NR	NR
Pruritus	20 (14.9)	10 (14.9)	NR	NR
Fatigue	11 (8.2)	10 (14.9)	NR	NR
Headache	15 (11.2)	4 (6)	NR	NR
Muscle spasms	11 (8.2)	4 (6)	NR	NR
Back pain	10 (7.5)	2 (3)	NR	NR
Cough	10 (7.5)	3 (4.5)	NR	NR
Bone pain	10 (7.5)	4 (6)	NR	NR
Urinary tract infection	10 (7.5)	4 (6)	NR	NR
Dyspnoea	18 (13.4)	4 (6)	NR	NR
Pyrexia	18 (13.4)	7 (10.4)	NR	NR
Abdominal pain	16 (11.9)	9 (13.4)	NR	NR
Abdominal pain upper	6 (4.5)	6 (9)	NR	NR
Abdominal discomfort	5 (3.7)	4 (6)	NR	NR
ALT increased	11 (8.2)	1 (1.5)	10 (7.5)	0
AST increased	7 (5.2)	0	NR	NR
Pneumonia	6 (4.5)	5 (7.5)	NR	NR
Hyperhidrosis	4 (3)	4 (6)	NR	NR
Hyperuricaemia	9 (6.7)	1 (1.5)	NR	NR
Hyperkalaemia	16 (11.9)	0	NR	NR
Hypokalaemia	7 (5.2)	2 (3)	NR	NR
Insomnia	7 (5.2)	4 (6)	NR	NR
Pain in extremity	7 (5.2)	1 (1.5)	NR	NR
Acute kidney injury	11 (8.2)	1 (1.5)	NR	NR
Chronic kidney disease	7 (5.2)	0	NR	NR
Blood creatinine increased	17 (12.7)	1 (1.5)	10 (7.5)	0
Decreased appetite	17 (12.7)	9 (13.4)	NR	NR
Vitamin B1 decreased	17 (12.7)	2 (3)	11 (8.2)	0

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	Treatment-emergent		Treatment-related	
	Fedratinib (n = 134)	BAT (n = 67)	Fedratinib (n = 134)	BAT (n = 67)
Vitamin B1 deficiency	10 (7.5)	1 (1.5)	7 (5.2)	0
Neutropenia	9 (6.7)	2 (3)	NR	NR
Weight decreased	9 (6.7)	0	NR	NR
Arthralgia	8 (6)	4 (6)	NR	NR
Epistaxis	8 (6)	0	NR	NR
Night sweats	8 (6)	9 (13.4)	NR	NR
General physical health deterioration	13 (9.7)	2 (3)	NR	NR
Glomerular filtration rate decreased	12 (9)	1 (1.5)	NR	NR
Atrial fibrillation	7 (5.2)	0	NR	NR
Renal failure	7 (5.2)	0	NR	NR

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BAT = best available therapy; NR = not reported; TEAE = treatment-emergent adverse event.

Notes: Shown are any AEs with onset or worsening in grade between the date of the first dose and 30 days after the date of last dose occurring in more than 5% of participants in either arm.

For the fedratinib arm, only participants who initially were randomly assigned to fedratinib are included. For crossover participants in BAT arm, only data before crossover are included.

Source: BMS data on file[45]

Table 29. FREEDOM-2: common treatment-emergent and treatment-related adverse events (crossover fedratinib population)

	Treatment-emergent	Treatment-related
	Crossover fedratinib (n = 46)	
Participants with at least 1 TEAE	46 (100)	38 (82.6)
Anaemia	20 (43.5)	14 (30.4)
Thrombocytopenia	13 (28.3)	10 (21.7)
Diarrhoea	17 (37.0)	15 (32.6)
Nausea	11 (23.9)	11 (23.9)
Vomiting	9 (19.6)	7 (15.2)
Constipation	6 (13)	NR
Asthenia	8 (17.4)	NR
Oedema peripheral	6 (13)	NR
COVID-19	12 (26.1)	NR
Pruritus	5 (10.9)	NR
Fatigue	4 (8.7)	NR
Dizziness	4 (8.7)	NR
Headache	3 (6.5)	NR
Cough	5 (10.9)	NR
Urinary tract infection	5 (10.9)	NR
Dyspnoea	6 (13)	NR
Pyrexia	4 (8.7)	NR
Abdominal pain	7 (15.2)	NR

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	Treatment-emergent	Treatment-related
	Crossover fedratinib (n = 46)	
Pneumonia	4 (8.7)	3 (6.5)
Chronic kidney disease	3 (6.5)	NR
Conjunctival haemorrhage	3 (6.5)	NR
Blood creatinine increased	4 (8.7)	NR
Decreased appetite	3 (6.5)	NR
Vitamin B1 decreased	4 (8.7)	NR
Neutropenia	4 (8.7)	NR
Weight decreased	3 (6.5)	NR
Arthralgia	4 (8.7)	NR
Epistaxis	3 (6.5)	NR
Night sweats	7 (15.2)	NR
Fall	3 (6.5)	NR
Gastroesophageal reflux disease	3 (6.5)	NR
Haematoma	3 (6.5)	NR
Renal failure	3 (6.5)	3 (6.5)

AE = adverse event; NR = not reported; TEAE = treatment-emergent adverse event.

Note: Shown are any AEs with onset or worsening in grade between the date of the first dose and 30 days after the date of last dose occurring in more than 5% of participants.

Source: BMS data on file[45]

B.2.10.4 Treatment-emergent serious adverse events

B.2.10.4.1 FREEDOM-2

Treatment-emergent serious AEs (SAEs) were reported in 72 participants (53.7%) in the fedratinib all-treated population, 21 (31.3%) in the BAT all-treated population, and 16 (34.8%) in the fedratinib crossover arm. The most common SAE was infections and infestations, reported in 17 participants (12.7%) in the fedratinib all-treated arm and 10 (14.9%) in the BAT all-treated arm. For the fedratinib crossover population, the most common SAE was also infections and infestations, reported in 9 participants (19.6%).

Treatment-related SAEs were reported in 25 participants (18.7%) in the fedratinib all-treated population, 2 (3%) in the BAT all-treated population, and 5 (10.9%) in the fedratinib crossover arm. The most common SAE was renal and urinary disorders, reported in 8 participants (6%) in the fedratinib all-treated population. The 2 SAEs in the BAT arm reported were a respiratory, thoracic, and mediastinal disorder (pleural effusion) and an infection and infestation (lymph node tuberculosis). For the fedratinib crossover population, the most common SAE was infections and infestations, reported in only 2 participants (4.3%).

A summary of treatment-emergent and treatment-related SAEs is presented in Table 30 for all-treated fedratinib and BAT populations and in Table 31 for the fedratinib crossover population.

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Table 30. FREEDOM-2: treatment-emergent and treatment-related SAEs (all-treated population)

	Treatment-emergent		Treatment-related	
System Organ Class, Preferred Term, n (%)	Fedratinib (n = 134)	BAT (n = 67)	Fedratinib (n = 134)	BAT (n = 67)
Participants with ≥ 1 SAE	72 (53.7)	21 (31.3)	25 (18.7)	2 (3)
Gastrointestinal disorders	13 (9.7)	1 (1.5)	4 (3)	0
Vomiting	1 (0.7)	0	1 (0.7)	0
Abdominal pain	2 (1.5)	0	1 (0.7)	0
Abdominal pain upper	0	1 (1.5)	NR	NR
Gastrointestinal haemorrhage	2 (1.5)	0	NR	NR
Ascites	1 (0.7)	0	NR	NR
Constipation	1 (0.7)	0	NR	NR
Duodenal ulcer	1 (0.7)	0	NR	NR
Gastric ulcer	1 (0.7)	0	NR	NR
Intestinal obstruction	1 (0.7)	0	NR	NR
Melaena	1 (0.7)	0	NR	NR
Subileus	1 (0.7)	0	1 (0.7)	0
Upper gastrointestinal haemorrhage	1 (0.7)	0	1 (0.7)	0
Varices oesophageal	1 (0.7)	0	NR	NR
Renal and urinary disorders	12 (9)	3 (4.5)	8(6)	0
Acute kidney injury	7 (5.2)	1 (1.5)	4 (3)	0
Chronic kidney disease	2 (1.5)	0	2 (1.5)	0
Renal failure	2 (1.5)	0	2 (1.5)	0
Bladder outlet obstruction	1 (0.7)	0	NR	NR
Haematuria	1 (0.7)	0	NR	NR
Calculus urinary	0	1 (1.5)	NR	NR
Renal colic	0	1 (1.5)	NR	NR
Investigations	3 (2.2)	0	NR	NR
ALT increased	1 (0.7)	0	NR	NR
AST increased	1 (0.7)	0	NR	NR
Ejection fraction decreased	1 (0.7)	0	NR	NR
Liver function test abnormal	1 (0.7)	0	NR	NR
Blood and lymphatic system disorders	11 (8.2)	4 (6)	5 (3.7)	0
Thrombocytopenia	2 (1.5)	0	1 (0.7)	0
Anaemia	9 (6.7)	0	4 (3)	0
Leukocytosis	1 (0.7)	2 (3)	NR	NR
Splenic infarction	0	1 (1.5)	NR	NR
Spontaneous haematoma	0	1 (1.5)	NR	NR
Cardiac disorders	13 (9.7)	1 (1.5)	2 (1.5)	0
Cardiac failure	4 (3)	1 (1.5)	NR	NR
Atrial fibrillation	3 (2.2)	0	2 (1.5)	0
Cardiac failure congestive	3 (2.2)	0	NR	NR
Cardiac arrest	2 (1.5)	0	NR	NR
Right ventricular failure	1 (0.7)	0	NR	NR
Infections and infestations	17 (12.7)	10 (14.9)	1 (0.7)	1 (1.5)
Pneumonia	3 (2.2)	3 (4.5)	NR	NR
COVID-19	2 (1.5)	3 (4.5)	NR	NR
Escherichia sepsis	2 (1.5)	0	1 (0.7)	0

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System Organ Class, Preferred Term, n (%)	Treatment-emergent		Treatment-related	
	Fedratinib (n = 134)	BAT (n = 67)	Fedratinib (n = 134)	BAT (n = 67)
COVID-19 pneumonia	1 (0.7)	2 (3)	NR	NR
Cellulitis	1 (0.7)	0	NR	NR
Cholecystitis infective	1 (0.7)	1 (1.5)	NR	NR
Epididymitis	1 (0.7)	0	NR	NR
Lower respiratory tract infection	1 (0.7)	0	NR	NR
Neutropenic sepsis	1 (0.7)	0	NR	NR
Pneumonia bacterial	1 (0.7)	0	NR	NR
Postoperative wound infection	1 (0.7)	0	NR	NR
Respiratory tract infection	1 (0.7)	1 (1.5)	NR	NR
Sepsis	1 (0.7)	0	NR	NR
Septic shock	1 (0.7)	0	NR	NR
Soft tissue infection	1 (0.7)	0	NR	NR
Streptococcal bacteraemia	1 (0.7)	0	NR	NR
Tuberculosis	1 (0.7)	0	NR	NR
Urinary tract infection	1 (0.7)	0	NR	NR
Urinary tract infection bacterial	1 (0.7)	0	NR	NR
Bronchitis	0	1 (1.5)	NR	NR
Lymph node tuberculosis	0	1 (1.5)	0	1 (1.5)
Peritonitis	0	1 (1.5)	NR	NR
General disorders and administration site conditions	15 (11.2)	3 (4.5)	2 (1.5)	0
General physical health deterioration	10 (7.5)	1 (1.5)	2 (1.5)	0
Multiple organ dysfunction syndrome	2 (1.5)	0	NR	NR
Exercise tolerance decreased	1 (0.7)	0	NR	NR
Oedema peripheral	1 (0.7)	0	NR	NR
Pyrexia	1 (0.7)	1 (1.5)	NR	NR
Asthenia	0	1 (1.5)	NR	NR
Injury, poisoning, and procedural complications	5 (3.7)	1 (1.5)	NR	NR
Fall	2 (1.5)	0	NR	NR
Postprocedural haemorrhage	1 (0.7)	0	NR	NR
Spinal compression fracture	1 (0.7)	0	NR	NR
Traumatic haematoma	1 (0.7)	0	NR	NR
Traumatic intracranial haemorrhage	1 (0.7)	0	NR	NR
Skin laceration	0	1 (1.5)	NR	NR
Metabolism and nutrition disorders	7 (5.2)	1 (1.5)	3 (2.2)	0
Hyperkalaemia	2 (1.5)	0	1 (0.7)	0
Vitamin B1 deficiency	2 (1.5)	0	2 (1.5)	0
Gout	1 (0.7)	0	NR	NR
Hyperuricaemia	1 (0.7)	0	NR	NR
Hyponatraemia	1 (0.7)	0	NR	NR
Tumour lysis syndrome	0	1 (1.5)	NR	NR
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	4 (3)	1 (1.5)	1 (0.7)	0
Squamous cell carcinoma of skin	2 (1.5)	0	1 (0.7)	0
Adenocarcinoma gastric	1 (0.7)	0	NR	NR
Adenocarcinoma of colon	1 (0.7)	0	NR	NR
Malignant melanoma	1 (0.7)	0	NR	NR

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System Organ Class, Preferred Term, n (%)	Treatment-emergent		Treatment-related	
	Fedratinib (n = 134)	BAT (n = 67)	Fedratinib (n = 134)	BAT (n = 67)
Penile cancer	1 (0.7)	0	NR	NR
Squamous cell carcinoma	1 (0.7)	0	NR	NR
Adrenal neoplasm	0	1 (1.5)	NR	NR
Nervous system disorders	2 (1.5)	1 (1.5)	NR	NR
Cerebral haemorrhage	1 (0.7)	0	NR	NR
Metabolic encephalopathy	1 (0.7)	0	NR	NR
Sciatica	0	1 (1.5)	NR	NR
Vascular disorders	3 (2.2)	2 (3)	NR	NR
Aortic aneurysm	2 (1.5)	0	NR	NR
Haemorrhage	1 (0.7)	0	NR	NR
Aortic dissection	0	1 (1.5)	NR	NR
Haematoma	0	1 (1.5)	NR	NR
Eye disorders	6 (4.5)	0	2 (1.5)	0
Uveitis	2 (1.5)	0	1 (0.7)	0
Cataract	1 (0.7)	0	NR	NR
Iridocyclitis	1 (0.7)	0	1 (0.7)	0
Retinal oedema	1 (0.7)	0	NR	NR
Vitreous haemorrhage	1 (0.7)	0	NR	NR
Respiratory, thoracic, and mediastinal disorders	6 (4.5)	5 (7.5)	1 (0.7)	1 (1.5)
Dyspnoea	3 (2.2)	0	1 (0.7)	0
Acute respiratory failure	1 (0.7)	0	NR	NR
Emphysema	1 (0.7)	0	NR	NR
Organising pneumonia	1 (0.7)	0	NR	NR
Pulmonary oedema	1 (0.7)	0	NR	NR
Lung infiltration	0	1 (1.5)	NR	NR
Pleural effusion	0	1 (1.5)	0	1 (1.5)
Pulmonary embolism	0	1 (1.5)	NR	NR
Respiratory distress	0	1 (1.5)	NR	NR
Respiratory failure	0	1 (1.5)	NR	NR
Hepatobiliary disorders	2 (1.5)	0	NR	NR
Cholecystitis acute	1 (0.7)	0	NR	NR
Hepatosplenomegaly	1 (0.7)	0	NR	NR
Musculoskeletal and connective tissue disorder	1 (0.7)	1 (1.5)	NR	NR
Bursitis	1 (0.7)	0	NR	NR
Arthralgia	0	1 (1.5)	NR	NR
Psychiatric disorder	1 (0.7)	0	NR	NR
Delirium febrile	1 (0.7)	0	NR	NR
Reproductive system and breast disorders	1 (0.7)	0	NR	NR
Breast fibrosis	1 (0.7)	0	NR	NR
Endocrine disorders	0	1 (1.5)	NR	NR
Adrenal haemorrhage	0	1 (1.5)	NR	NR

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BAT = best available therapy; NR = not reported; SAE = serious adverse event.

Note: Shown are any AEs with onset or worsening in grade between the date of the first dose and 30 days after the date of last dose.

Source: BMS data on file[45]

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Table 31. FREEDOM-2: treatment-emergent and treatment-related SAEs (crossover fedratinib population)

	Treatment-emergent	Treatment-related
System Organ Class, Preferred Term, n (%)	**Crossover fedratinib (n = 46)**	
Participants with ≥ 1 SAE	16 (34.8)	5 (10.9)
Gastrointestinal disorders	3 (6.5)	NR
Abdominal pain	1 (2.2)	NR
Abdominal pain upper	1 (2.2)	NR
Duodenal ulcer haemorrhage	1 (2.2)	NR
Renal and urinary disorders	1 (2.2)	NR
Haematuria	1 (2.2)	NR
Blood and lymphatic system disorders	2 (4.3)	1 (2.2)
Thrombocytopenia	1 (2.2)	NR
Anaemia	2 (4.3)	1 (2.2)
Infections and infestations	9 (19.6)	2 (4.3)
Pneumonia	2 (4.3)	1 (2.2)
COVID-19	3 (6.5)	NR
Abscess soft tissue	1 (2.2)	NR
Clostridium difficile infection	1 (2.2)	NR
Perineal abscess	1 (2.2)	NR
Sinusitis	1 (2.2)	1 (2.2)
Urinary tract infection	3 (6.5)	NR
General disorders and administration site conditions	2 (4.3)	NR
General physical health deterioration	1 (2.2)	NR
Pyrexia	1 (2.2)	NR
Injury, poisoning, and procedural complications	1 (2.2)	NR
Contusion	1 (2.2)	NR
Metabolism and nutrition disorders	1 (2.2)	1 (2.2)
Hypocalcaemia	1 (2.2)	1 (2.2)
Tumour lysis syndrome	1 (2.2)	1 (2.2)
Nervous system disorders	2 (4.3)	1 (2.2)
Headache	1 (2.2)	NR
Extrapyramidal disorder	1 (2.2)	1 (2.2)
Vascular disorders	1 (2.2)	NR
Haematoma	1 (2.2)	NR
Respiratory, thoracic, and mediastinal disorders	1 (2.2)	1 (2.2)
Dyspnoea	1 (2.2)	1 (2.2)

AE = adverse event; NR = not reported; SAE = serious adverse event.

Note: Shown are any AEs with onset or worsening in grade between the date of the first dose and 30 days after the date of last dose.

Source: BMS data on file[45]

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B.2.10.5 Adverse events leading to treatment discontinuation

B.2.10.5.1 FREEDOM-2

Treatment-emergent AEs leading to permanent treatment discontinuation occurred in 24 participants (17.9%) in the fedratinib population, 4 (6%) in the BAT all-treated population, and 7 (15.2%) in the fedratinib crossover population. The most common reason for treatment discontinuation for the fedratinib all-treated population was blood and lymphatic system disorders, which occurred in 5 participants (3.7%), followed by renal and urinary disorders in 4 participants (3%). In the BAT all-treated arm, the most common reason for treatment discontinuation was infections and infestations, which occurred in 2 participants (3%). The most common reasons for treatment discontinuation in the fedratinib crossover population were blood and lymphatic system disorders and infections and infestations, which occurred in 2 participants (4.3%) in each of those System Organ Classes. Table 32 summarises TEAEs leading to permanent treatment discontinuation in FREEDOM-2.

Table 32. FREEDOM-2: TEAEs leading to treatment discontinuation (all-treated and crossover population)

	All-treated		Crossover
System Organ Class, Preferred Term, n (%)[a]	**Fedratinib (n = 134)**	**BAT (n = 67)**	**Fedratinib (n = 46)**
Participants with ≥ 1 TEAE leading to permanent treatment discontinuation	24 (17.9)	4 (6.0)	7 (15.2)
Gastrointestinal disorders	3 (2.2)	0	1 (2.2)
Diarrhoea	1 (0.7)	0	1 (2.2)
Abdominal pain	1 (0.7)	0	NR
Nausea	1 (0.7)	0	NR
Vomiting	1 (0.7)	0	NR
Renal and urinary disorders	4 (3.0)	0	NR
Chronic kidney disease	2 (1.5)	0	NR
Acute kidney injury	2 (1.5)	0	NR
Blood and lymphatic system disorders	5 (3.7)	1 (1.5)	2 (4.3)
Neutropenia	1 (0.7)	0	NR
Thrombocytopenia	2 (1.5)	0	2 (4.3)
Leukocytosis	1 (0.7)	1 (1.5)	NR
Anaemia	1 (0.7)	0	NR
Cardiac disorders	1 (0.7)	0	NR
Cardiac arrest	1 (0.7)	0	NR
Infections and infestations	0	2 (3.0)	2 (4.3)
Pneumonia	0	1 (1.5)	NR
Lymph node tuberculosis	0	1 (1.5)	NR
COVID-19	NR	NR	1 (2.2)
Clostridium difficile infection	NR	NR	1 (2.2)
General disorders and administration site conditions	4 (3.0)	0	NR
Asthenia	1 (0.7)	0	NR
General physical health deterioration	2 (1.5)	0	NR

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System Organ Class, Preferred Term, n (%)[a]	All-treated		Crossover
	Fedratinib (n = 134)	BAT (n = 67)	Fedratinib (n = 46)
Oedema peripheral	1 (0.7)	0	NR
Hepatobiliary disorders	1 (0.7)	0	NR
Hepatosplenomegaly	1 (0.7)	0	NR
Metabolism and nutrition disorders	1 (0.7)	0	NR
Hyperuricaemia	1 (0.7)	0	NR
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	3 (2.2)	0	1 (2.2)
Adenocarcinoma gastric	1 (0.7)	0	NR
Squamous cell carcinoma	1 (0.7)	0	NR
Transformation to AML	1 (0.7)	0	1 (2.2)
Eye disorders	2 (1.5)	0	NR
Iridocyclitis	1 (0.7)	0	NR
Uveitis	1 (0.7)	0	NR
Nervous system disorders	2 (1.5)	0	1 (2.2)
Peripheral sensory neuropathy	1 (0.7)	0	NR
Wernicke's encephalopathy	1 (0.7)	0	NR
Extrapyramidal disorder	NR	NR	1 (2.2)
Skin and subcutaneous tissue disorders	0	1 (1.5)	NR
Skin ulcer	0	1 (1.5)	NR

AE = adverse event; AML = acute myeloid leukaemia; BAT = best available therapy; MedDRA = Medical Dictionary for Regulatory Activities; NR = not reported; TEAE = treatment-emergent adverse event.

Note: Shown are any AEs with onset or worsening in grade between the date of the first dose and 30 days after the date of last dose.

[a] System Organ Class and Preferred Terms were coded using the MedDRA version 25.1. If multiple TEAEs were reported within a given Preferred Term, only 1 event was counted per participant. The table is sorted by decreasing frequency of System Organ Class and Preferred Term in the all-grades column of TEAEs (without consideration of relatedness).

Source: BMS data on file[45]

Table 33. FREEDOM-2: TEAEs leading to dose reduction and interruption (all-treated population)

System Organ Class, Preferred Term, n (%)	Dose reduction		Dose interruption	
	Fedratinib (n = 134)	BAT (n = 67)	Fedratinib (n = 134)	BAT (n = 67)
Participants with ≥ 1 TEAE leading to dose modification	48 (35.8)	7 (10.4)	52 (38.8)	4 (6)
Gastrointestinal disorders	6 (4.5)	0	15 (11.2)	1 (1.5)
Diarrhoea	1 (0.7)	0	7 (5.2)	0
Abdominal pain upper	1 (0.7)	0	NR	NR
Abdominal pain	NR	NR	2 (1.5)	0
Nausea	3 (2.2)	0	2 (1.5)	1 (1.5)
Vomiting	1 (0.7)	0	2 (1.5)	0
Ascites	1 (0.7)	0	NR	NR

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System Organ Class, Preferred Term, n (%)	Dose reduction		Dose interruption	
	Fedratinib (n = 134)	BAT (n = 67)	Fedratinib (n = 134)	BAT (n = 67)
Gastrointestinal haemorrhage	1 (0.7)	0	1 (0.7)	0
Constipation	1 (0.7)	0	1 (0.7)	0
Duodenal ulcer	NR	NR	1 (0.7)	0
Dyspepsia	NR	NR	1 (0.7)	0
Melaena	NR	NR	1 (0.7)	0
Subileus	NR	NR	1 (0.7)	0
Upper gastrointestinal haemorrhage	NR	NR	1 (0.7)	0
Varices oesophageal	NR	NR	1 (0.7)	0
Renal and urinary disorders	11 (8.2)	0	8 (6)	0
Chronic kidney disease	4 (3)	0	NR	NR
Acute kidney injury	4 (3)	0	2 (1.5)	0
Renal failure	2 (1.5)	0	2 (1.5)	0
Renal impairment	2 (1.5)	0	3 (2.2)	0
Renal colic	NR	NR	1 (0.7)	0
Infections and infestations	NR	NR	8 (6)	0
Bronchitis	NR	NR	1 (0.7)	0
COVID-19	NR	NR	1 (0.7)	0
COVID-19 pneumonia	NR	NR	1 (0.7)	0
Cellulitis	NR	NR	1 (0.7)	0
Cholecystitis infective	NR	NR	1 (0.7)	0
Escherichia sepsis	NR	NR	1 (0.7)	0
Pneumonia bacterial	NR	NR	1 (0.7)	0
Sepsis	NR	NR	1 (0.7)	0
Tuberculosis	NR	NR	1 (0.7)	0
Blood and lymphatic system disorders	21 (15.7)	7 (10.4)	14 (10.4)	2 (3)
Neutropenia	3 (2.2)	0	NR	NR
Thrombocytopenia	16 (11.9)	3 (4.5)	12 (9)	1 (1.5)
Anaemia	4 (3)	5 (7.5)	2 (1.5)	2 (3)
Cardiac disorders	1 (0.7)	0	2 (1.5)	0
Cardiac failure	1 (0.7)	0	1 (0.7)	0
Atrial fibrillation	NR	NR	1 (0.7)	0
General disorders and administration site conditions	4 (3)	0	5 (3.7)	0
Asthenia	2 (1.5)	0	3 (2.2)	0
General physical health deterioration	NR	NR	2 (1.5)	0
Fatigue	1 (0.7)	0	NR	NR
Oedema peripheral	1 (0.7)	0	NR	NR
Metabolism and nutrition disorders	1 (0.7)	0	6 (4.5)	2 (3)
Hyponatraemia	1 (0.7)	0	1 (0.7)	0
Hyperkalaemia	NR	NR	5 (3.7)	0

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System Organ Class, Preferred Term, n (%)	Dose reduction		Dose interruption	
	Fedratinib (n = 134)	BAT (n = 67)	Fedratinib (n = 134)	BAT (n = 67)
Hypomagnesaemia	NR	NR	1 (0.7)	0
Gout	NR	NR	0	1 (1.5)
Hypercalcaemia	NR	NR	0	1 (1.5)
Eye disorders	1 (0.7)	0	3 (2.2)	0
Retinal oedema	1 (0.7)	0	1 (0.7)	0
Dry eye	NR	NR	1 (0.7)	0
Lacrimation increased	NR	NR	1 (0.7)	0
Nervous system disorders	1 (0.7)	0	NR	NR
Peripheral sensory neuropathy	1 (0.7)	0	NR	NR
Investigations	9 (6.7)	0	7 (5.2)	0
ALT increased	3 (2.2)	0	3 (2.2)	0
Blood creatinine increased	3 (2.2)	0	3 (2.2)	0
Vitamin B1 decreased	2 (1.5)	0	NR	NR
Glomerular filtration rate decreased	1 (0.7)	0	1 (0.7)	0
Glomerular filtration rate increased	1 (0.7)	0	NR	NR
Liver function test abnormal	NR	NR	1 (0.7)	0
AST increased	NR	NR	2 (1.5)	0
Respiratory, thoracic, and mediastinal disorders	1 (0.7)	0	1 (0.7)	0
Organising pneumonia	NR	NR	1 (0.7)	0
Dyspnoea	1 (0.7)	0	NR	NR
Vascular disorder	NR	NR	2 (1.5)	0
Aortic aneurysm	NR	NR	1 (0.7)	0
Haemorrhage	NR	NR	1 (0.7)	0
Injury, poisoning, and procedural complications	NR	NR	1 (0.7)	1 (1.5)
Fall	NR	NR	1 (0.7)	0
Contusion	NR	NR	0	1 (1.5)

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BAT = best available therapy; NR = not reported; TEAE = treatment-emergent adverse event.

Note: Shown are any AEs with onset or worsening in grade between the date of the first dose and 30 days after the date of last dose.

Source: BMS data on file[45]

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Table 34. FREEDOM-2: TEAEs leading to dose reduction and interruption (crossover fedratinib population)

	Dose reduction	Dose interruption
System Organ Class, Preferred Term, n (%)	**Crossover fedratinib (n = 46)**	
Participants with ≥ 1 TEAE leading to dose modification	18 (39.1)	15 (32.6)
Gastrointestinal disorders	1 (2.2)	6 (13)
Diarrhoea	NR	3 (6.5)
Abdominal pain	1 (2.2)	NR
Nausea	NR	2 (4.3)
Vomiting	NR	3 (6.5)
Renal and urinary disorders	5 (10.9)	3 (6.5)
Chronic kidney disease	1 (2.2)	1 (2.2)
Renal failure	2 (4.3)	1 (2.2)
Renal impairment	2 (4.3)	1 (2.2)
Infections and infestations	NR	3 (6.5)
COVID-19	NR	2 (4.3)
Urinary tract infection	NR	1 (2.2)
Blood and lymphatic system disorders	11 (23.9)	4 (8.7)
Neutropenia	NR	1 (2.2)
Thrombocytopenia	4 (8.7)	2 (4.3)
Anaemia	7 (15.2)	1 (2.2)
General disorders and administration site conditions	NR	1 (2.2)
Asthenia	NR	1 (2.2)
Metabolism and nutrition disorders	2 (4.3)	1 (2.2)
Hyperkalaemia	1 (2.2)	NR
Hypocalcaemia	NR	1 (2.2)
Tumour lysis syndrome	1 (2.2)	NR
Respiratory, thoracic, and mediastinal disorders	1 (2.2)	2 (4.3)
Dyspnoea	1 (2.2)	1 (2.2)
Laryngeal haemorrhage	NR	1 (2.2)
Vascular disorder	1 (2.2)	NR
Haematoma	1 (2.2)	NR
Skin and subcutaneous tissue disorders	1 (2.2)	NR
Dry skin	1 (2.2)	NR
Hepatobiliary disorders	NR	1 (2.2)
Hepatotoxicity	NR	1 (2.2)

AE = adverse event; NR = not reported; TEAE = treatment-emergent adverse event.

Note: Shown are any AEs with onset or worsening in grade between the date of the first dose and 30 days after the date of last dose.

Source: BMS data on file[45]

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B.2.10.6 Adverse events leading to death

In FREEDOM-2, a total of 21 participants (15.7%) on fedratinib, 4 (6%) in the BAT arm, and 4 (8.7%) who crossed over to fedratinib from BAT died during the treatment course.[36] Table 35 summarises TEAEs leading to death.

Table 35. FREEDOM-2: TEAEs leading to death (all-treated population and crossover population)

System Organ Class, Preferred Term, n (%)[a]	Fedratinib (n = 134)	BAT (n = 67)	Crossover fedratinib (n = 46)
Participants with ≥ 1 TEAE leading to death	21 (15.7)	4 (6.0)	4 (8.7)
General disorders and administration site conditions	10 (7.5)	1 (1.5)	NR
Multiple organ dysfunction syndrome	2 (1.5)	0	NR
General physical health deterioration	8 (6.0)	1 (1.5)	NR
Infections and infestations	3 (2.2)	3 (4.5)	4 (8.7)
Pneumonia	0	2 (3.0)	NR
Sepsis	1 (0.7)	0	NR
Septic shock	1 (0.7)	0	NR
COVID-19	0	1 (1.5)	3 (6.5)
COVID-19 pneumonia	1 (0.7)	1 (1.5)	NR
Clostridium difficile infection	NR	NR	1 (2.2)
Cardiac disorders	2 (1.5)	0	NR
Cardiac arrest	2 (1.5)	0	NR
Injury, poisoning, and procedural complications	2 (1.5)	0	NR
Fall	1 (0.7)	0	NR
Traumatic intracranial haemorrhage	1 (0.7)	0	NR
Respiratory, thoracic, and mediastinal disorders	1 (0.7)	0	NR
Respiratory failure	1 (0.7)	0	NR
Vascular disorders	1 (0.7)	0	NR
Aortic aneurysm	1 (0.7)	0	NR
Nervous system disorders	1 (0.7)	0	NR
Cerebral haemorrhage	1 (0.7)	0	NR
Renal and urinary disorders	1 (0.7)	0	NR
Acute kidney injury	1 (0.7)	0	NR

AE = adverse event; BAT = best available therapy; MedDRA = Medical Dictionary for Regulatory Activities; NR = not reported; TEAE = treatment-emergent adverse event.

Notes: Shown are any AEs with onset or worsening in grade between the date of the first dose and 30 days after the date of last dose.

The table is sorted by decreasing frequency of System Organ Class and Preferred Term.

[a] System Organ Classes and Preferred Terms were coded using the MedDRA version 25.1. If multiple TEAEs were reported within a given Preferred Term, only 1 event was counted per participant.

Source: FREEDOM-2 CSR[45]

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B.2.10.7 Safety overview

B.2.10.7.1 FREEDOM-2

The safety results of FREEDOM-2 were also aligned with the known profile of fedratinib. The mitigation strategies for gastrointestinal and thiamine-related toxicities were generally effective.[36] Within the first 6 treatment cycles, there were similar rates of at least 1 TEAE each reported in the fedratinib and BAT treatment arms. Grade 3 or 4 TEAEs related to the study drug were reported for 38.8% of participants in the fedratinib arm and 11.9% in the BAT arm. Permanent discontinuation of the study drug resulted from TEAEs in 9.7% of participants in the fedratinib arm and 6.0% in the BAT arm.[36]

During the full treatment period, 98.5% of participants in the fedratinib arm and 97.0% in the BAT arm had at least 1 TEAE. Grade 3 or 4 TEAEs related to the study drug were reported for 46.3% of participants in the fedratinib arm and 14.9% in the BAT arm. Permanent discontinuation of the study drug resulted from TEAEs in 17.9% of participants in the fedratinib arm and 6.0% in the BAT arm.[36]

B.2.11 Ongoing studies

The phase 3 FREEDOM-2 study of fedratinib compared with BAT in participants with DIPSS intermediate or high-risk PMF, post-PV MF, or post-ET MF who were previously treated with ruxolitinib is currently ongoing but no longer recruiting. The primary clinical study report was finalised in August 2023. The estimated completion date is June 2025.

B.2.12 Interpretation of clinical effectiveness and safety evidence

FREEDOM-2 demonstrated that treatment with fedratinib, compared with BAT, is associated with considerable reductions in spleen volume and size, as well as marked improvements to symptoms in individuals previously treated with ruxolitinib.

Splenomegaly is the key physical feature and cause of symptoms of myelofibrosis; as such, SVR is an important treatment goal. Internationally recognised research groups have identified ≥ 35% SVR as the appropriate threshold for defining response in patients with myelofibrosis.[52] In FREEDOM-2, just over one-third of participants (35.8%) on fedratinib in FREEDOM-2 achieved this response versus 6% of participants on BAT.[36,53]

In lieu of availability of curative treatments, the relief of debilitating symptoms is another important treatment goal in myelofibrosis. The clinically meaningful threshold for symptom response is ≥ 50% reduction in TSS,[52] with 34.1% of participants receiving fedratinib in FREEDOM-2 having achieved this versus 16.9% of participants on BAT.[36,53] Alleviating these symptoms provides patients with an improved ability to carry out normal daily functions and relieves some of the physical and psychological burden associated with myelofibrosis.

Furthermore, the FREEDOM-2 subgroup analysis shows that treatment effects are consistent across all subgroups, such as baseline demographics, disease characteristics, platelet count, haemoglobin count, and ECOG PS.

Over the full course of the FREEDOM-2 study (full treatment period + crossover treatment period + follow-up period), death was reported for 43 participants (32.1%) in the fedratinib group and 18 (26.9%) in the BAT group.[36,45,48] There are clear methodological issues that may result in an underestimate of OS for the fedratinib group, which means that the OS data need to be considered with caution. In the participant population that received BAT, nearly 70% crossed over to fedratinib, leaving few participants in the BAT-only population, something the study was not powered for. Crossover analyses were attempted; however, none of the methods were suitable because they provided contradictory results

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and violated underlying assumptions. Therefore, the results of the crossover analysis are not considered reliable.

The proposed position of fedratinib in the treatment pathway is narrower than the marketing authorisation because the population of patients who have been treated with ruxolitinib represents the greatest unmet need in myelofibrosis for which the clinical and cost-effectiveness of fedratinib is most demonstrable. The survival outcomes in patients who have been treated with ruxolitinib are poor, with studies indicating a median OS of 13 to 16 months after ruxolitinib discontinuation.[10,18-20] Furthermore, should fedratinib be included in the current treatment landscape in NHS England, additional treatment options would be available for the heterogenous patient population with myelofibrosis.

B.3 Cost-effectiveness

B.3.1 Published cost-effectiveness studies

An SLR was performed for TA756, to identify published cost-effectiveness studies in myelofibrosis to support the development of a de novo economic model for fedratinib. Since the submission of TA756, no other pharmaceuticals have been approved by NICE for this indication. Therefore, no further evidence is anticipated to be found other than the pivotal trial FREEDOM-2 (providing head-to-head data); thus, an update of the SLR would not impact this submission. The search strategy and study selection criteria are described in detail in Appendix G.

In total, 1,126 potentially relevant articles were identified in database searches. After exclusion of irrelevant articles (n = 1,120) and the addition of relevant articles from bibliographic (n = 1) and health technology assessment (HTA) (n = 8) searches, a total of 15 publications were included. Because some studies were associated with multiple publications, secondary publications were combined; this resulted in inclusion of 9 studies identified from 15 publications.[10,54-61] A summary of the 9 cost-effectiveness studies identified by the SLR are presented in Appendix G.

B.3.2 Economic analysis

The SLR included 9 studies from 15 publications that investigated the cost-effectiveness of therapies in patients with myelofibrosis. All 9 studies assessed the cost-effectiveness of ruxolitinib relative to either BAT or placebo. The studies included 5 ruxolitinib HTA submission documents:

- Canada: Canadian Agency for Drugs and Technologies in Health (CADTH), 2013[59]
- Ireland: National Centre for Pharmacoeconomics (NCPE), 2013[60]
- England and Wales: National Institute for Health and Care Excellence (NICE), 2016[10]
- Scotland: Scottish Medicines Consortium (SMC), 2015[58]
- Australia: Pharmaceutical Benefits Advisory Committee (PBAC), 2015[57]

The remaining 4 studies were published in peer-reviewed journals.[54-56,61]

Where reported, alive health states were often defined by the treatment received (n = 3).[10,56,58] This tended to consist of ruxolitinib, BAT, or supportive care. Alternatively, response or non-response were used to define health states (n = 3).[57,60,61] One study included leukaemic transformation as a health state (n = 1).[61] The omission of AML as a distinct health state was queried by the evidence review group in NICE TA386 (ruxolitinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis).[10] Three studies did not explicitly report health states (n = 3).[54,55,59]

Where reported, effectiveness outcomes were informed by 1 or more of 3 studies: COMFORT-I,[62] COMFORT-II,[63] and NCT00509899.[64] The primary outcomes of COMFORT-I and COMFORT-II were

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≥ 35% reduction in spleen volume from baseline at 24 weeks and 48 weeks, respectively. COMFORT-I also investigated symptom response, as assessed by the TSS of the modified MFSAF v2.0. NCT00509899 measured the proportion of participants with ≥ 35% reduction in spleen volume from baseline at time intervals up to 48 weeks, and the change in TSS from baseline at 24 weeks. In the economic models, 6 studies used one or both of the COMFORT-I and COMFORT-II studies to inform treatment response.[10,55-58,60] One study used both COMFORT-II and NCT00509899, but did not leverage the symptom score data.[61] Another study used NCT00509899 trial data alone and considered both spleen volume and symptom response to produce their economic recommendations.[59] One study did not report the data source used.[54]

Cohort models were commonly applied (n = 5).[54-56,60,61] Patient-level discrete-event simulation (DES) was also leveraged (n = 2). Two studies did not report the model type (n = 2).

A single submission to NICE was made in myelofibrosis (TA386[10]) and a DES modelling approach was used to estimate cost-effectiveness of ruxolitinib. In line with the modelling approach used in NICE TA386[10] and in the previous submission of fedratinib (NICE TA756), this submission takes a similar DES modelling approach to evaluate the cost-effectiveness of fedratinib in patients with myelofibrosis who have been treated with ruxolitinib.

B.3.2.1 Patient population

The main population in the economic analysis comprises adults with disease-related splenomegaly caused by PMF, post-PV MF, or post-ET MF who have been treated with ruxolitinib and are classified as intermediate-2 or high risk by DIPSS.

The data used for this analysis were derived from the FREEDOM-2 clinical trial. FREEDOM-2 is an ongoing, phase 3, multicentre, randomised, 2-arm, open-label trial that included participants with intermediate-2 or high-risk PMF, post-PV MF, or post-essential thrombocythaemia myelofibrosis previously treated with ruxolitinib.[36] A top-level summary of the trial is given in Table 36. All analyses were performed using the 27 December 2022 data cut for FREEDOM-2.

Table 36. FREEDOM-2: summary of characteristics

	Study characteristics
Study design	Phase 3, multicentre, randomised, 2-arm, open-label study
Population	Participants with DIPSS intermediate or high-risk primary myelofibrosis, post-polycythaemia vera myelofibrosis, or post-essential thrombocythaemia myelofibrosis and previously treated with ruxolitinib
Number of participants	ITT, n = 201
Treatments	Intervention: fedratinib Comparator: BAT
Stratification factors	Stratification at randomisation according to: ▪ Spleen size by palpation: < 15 cm below LCM vs. ≥ 15 cm below LCM ▪ Platelets ≥ 50 to < 100 × 10^9/L vs. platelets ≥ 100 × 10^9/L ▪ Refractory or relapsed to ruxolitinib treatment vs. intolerance to ruxolitinib treatment
Study objectives	The primary objective of the study is to evaluate the percentage of participants with ≥ 35% SVR in the fedratinib and the BAT arms.
Crossover	Yes: Participants are allowed to cross over from BAT to the fedratinib arm after the cycle 6 response assessment or before the cycle 6 response assessment in the event of a confirmed progression of splenomegaly by MRI/CT scan.

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	Study characteristics
Study completion date	The expected duration of the entire study is approximately 5 years, which includes approximately 24 months to fully enrol, and 30 months for treatment and follow-up. The actual duration of the trial will depend on the median treatment duration for participants.
Data cut	27 December 2022

BAT = best available therapy; CT = computed tomography; DIPSS = Dynamic International Prognostic Scoring System; ITT = intention to treat; LCM = left costal margin; MRI = magnetic resonance imaging; SVR = spleen volume reduction.

B.3.2.1.1 Patient characteristics

The demographics and baseline disease characteristics in FREEDOM-2 are representative of a group of people with advanced myelofibrosis and a high disease burden, with 16.9% of participants having received prior anticancer therapies other than ruxolitinib for myelofibrosis. All participants in FREEDOM-2 had received prior treatment with ruxolitinib over at least 3 months.[36]

There were no notable differences between the characteristics of participants receiving BAT and those of the participants receiving fedratinib, with the median age being 70.0 years (range, 40-86) in the fedratinib arm and 68.0 years (range, 38-91) for the BAT arm. Male participants comprised 56.0% of the fedratinib arm and 44.8% of the BAT arm. Finally, height and weight were similar across both arms; participants in fedratinib had a median height of 168.0 cm (range, 146.2-192.0) compared with 165.0 cm (range, 144.0-191.0) in the BAT arm. Their median weight was 71.70 kg (range, 43.0-112.2) for the fedratinib arm and 66.20 kg (range, 45.5-108.0) for the BAT arm.

Table 37 presents the baseline characteristics in FREEDOM-2 used in the cost-effectiveness model.

Table 37. FREEDOM-2: baseline characteristics

Parameter	Fedratinib (n = 134)	BAT (n = 67)	Source
Age, years			FREEDOM-2 CSR, Table 5.3.1-1
Mean (SD)	68.7 (8.79)	67.6 (8.16)	
Median (range)	70.0 (40-86)	68.0 (38-91)	
Sex, n (%)			
Male	75 (56.0)	30 (44.8)	
Female	59 (44.0)	37 (55.2)	
Weight, kg			
Mean (SD)	71.63 (14.56)	69.21 (13.73)	FREEDOM-2 CSR, Table 5.3.1-2
Median (range)	71.70 (43.0-112.2)	66.20 (45.5-108.0)	

SD = standard deviation.

In the economic model, the median is used for age, height, and weight; it is considered to be closer to the true average value of a sample than the mean, which could be skewed because of outliers. Considering that the total median value was not available from FREEDOM-2, a weighted mean and median parameters based on both treatment arms has been calculated to be inputted into the model. The values currently used in the economic model are reported in Table 38.

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Table 38. Patient characteristics included in the economic model

Parameter	Value	Source
Weighted median age at baseline (years)	69.3	FREEDOM-2 CSR, Table 5.3.1-2
% male at baseline	52.2	FREEDOM-2 CSR, Table 5.3.1-2
Weighted median weight at baseline (kg)	69.87	FREEDOM-2 CSR, Table 5.3.1-2
Weighted median body surface area at baseline (m^2)	1.80	FREEDOM-2 CSR, Table 5.3.1-2 and Mosteller formula

CSR = clinical study report.

B.3.2.2 Model structure

B.3.2.2.1 Model type

The cost-effectiveness analysis for fedratinib was conducted using a DES model built in Excel.

DES modelling, in line with the approach taken in TA756 and TA386, allow for individual patient pathways to be estimated by sampling directly from time-to-event curves. When more than 1 event may occur (such as treatment discontinuation or death), event times for each event are sampled, and the event with the lowest sampled time is simulated as occurring next. An advantage of the DES approach is that it does not impose assumptions that force events to only occur at defined intervals known as "time cycles," which is the standard approach in cohort-based models and many patient-level simulations. This model type also enables "memory," meaning a patient's experience of a treatment pathway (both their previous health states or treatments received along with time in their current health state) is recorded for accurate calculations of costs, utilities, and transitions to future health states. Based on the feedback from the External Assessment Group (EAG) in NICE TA756, the cost-effectiveness model was further updated with a supportive care health state and worsening health utility over time, as well as the replacement of the palliative health state with a one-off end-of-life cost.

DES modelling allows enhanced tracking of patients, enables memory to be implemented in the model, and provides flexibility in dealing with transitions. As such, the DES structure allows users to track the patients' time in health states and implement the health utilities for responders after 4 weeks in the health state, which is one of the primary endpoints of the FREEDOM-2 clinical trial. In addition, use of a DES structure is more accurate than a simpler area-under-the-curve model because it allows for estimation of the precise time of events (as opposed to assuming that they occur at discrete time cycles) as well as capturing patient heterogeneity in these outcomes. A potential drawback of DES models is that they can be computationally intensive, but this is not the case for the adapted model. Finally, because of the possibility for the model to stratify between responders and non-responders, a decision was made to keep the initial DES model structure to accurately reflect the progression of the disease.

B.3.2.2.2 Model structure

Figure 36 shows the model structure. The health states in the model are divided into 4 categories: treatment states, response assessment states, progressed states, and end-of-life states. In the treatment states, patients receive either fedratinib or BAT. Patients accrue costs according to the treatment received and accrue quality-adjusted life-years (QALYs) in line with their response to treatment. Patients enter the response assessment state after 24 weeks of treatment with either fedratinib or BAT. Patients who discontinue treatment or die before reaching this state are labelled as "early discontinuation" or "early death." In the assessment state, patients undergo an instantaneous response assessment. The potential definitions of response used in the model are:

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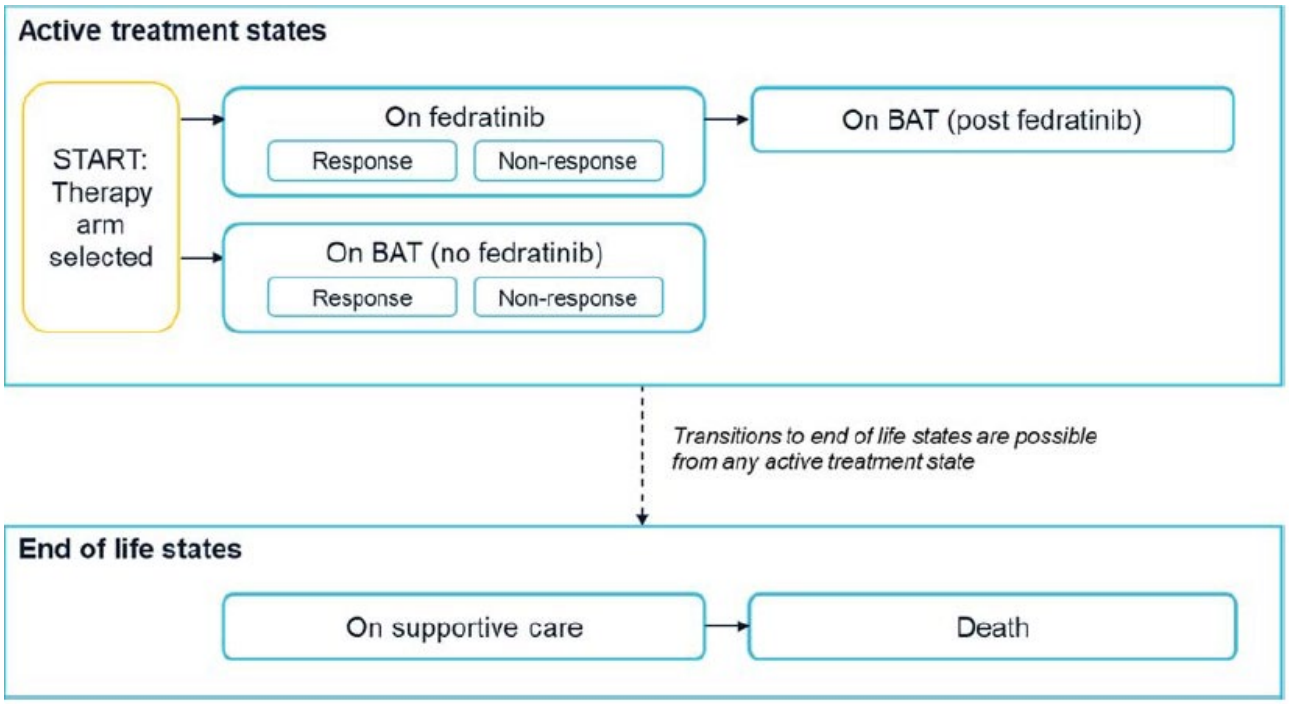
- Spleen volume reduction (SVR): ≥ 35% SVR from baseline at 24 weeks
- Symptom response (TSS): ≥ 50% TSS reduction from baseline at 24 weeks
- Spleen or symptom response: ≥ 35% spleen volume or ≥ 50% TSS reduction from baseline at 24 weeks

Further details on the response assessments are given in Section B.3.3. For both fedratinib and BAT, time to discontinuation beyond 24 weeks is estimated separately for responders and non-responders.

Figure 36. Model structure for fedratinib in myelofibrosis



BAT = best available therapy.

B.3.2.2.3 Model implementation

The model includes the explanation sheets (for model structure, model layout in Excel, background of the disease area), inputs and result sheets, as well as engine sheets. The user can set the settings of the model (i.e., time horizon, discounting, sources used in the model for survival, costs, and health utilities) in the 'Control' sheet. Most of the calculations are programmed in Visual Basic for Applications (VBA), which enables faster calculations. The VBA code contains several modules clearly labelled, with descriptions of the purpose and functioning of the code. The modelling methodology emulates from the approach taken in the previous technology appraisal of ruxolitinib (TA386)[10], the first JAK inhibitor approved for myelofibrosis, and remains the same as the modelling approach from the previous fedratinib in myelofibrosis NICE appraisal (TA756).[65]

Table 39 summarises the different events in the model and their descriptions.

Table 39. Implementation of events in the model

Event	Description	Assignment	Supporting data
Death (or early death)	The absorbing death state. 'Early death' is death before 24 weeks of treatment.	Time to death is sampled from parametric curves at the start of the simulation. No events can occur after death.	OS curves based on initial treatment

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Event	Description	Assignment	Supporting data
Response assessment	Patient undergoes response assessment at 24 weeks of treatment.	If a patient completed at least 24 weeks of treatment, they undergo a response assessment.	Structural model assumption informed by FREEDOM-2[36]
Response	Patient classified as a responder to treatment.	The proportion of responders is used to determine who responds at 24 weeks.	FREEDOM-2 clinical trial[36]
Non-response	Patient classified as a non-responder to treatment.	Patients who do not meet the criteria for response, as calculated above, are considered non-responders. If the stopping rule is used, the transition to BAT occurs immediately for these patients.	FREEDOM-2 clinical trial[36]
Discontinuation	Patient stops receiving fedratinib or BAT.	Time to discontinuation is sampled from parametric curves for responders and non-responders.	TTD curves
Worsening quality of life (both for fedratinib and BAT)	Patient receiving fedratinib and BAT experience a worsening quality of life over time, independent of age-related utility decline.	The health-state utility value applied to the patient is reduced every 24 weeks by a utility decrement. Only the utility changes, and the patient remains in the same health state.	The ruxolitinib appraisal (TA386)[10] in a JAK inhibitor–naive setting and initial appraisal of fedratinib in myelofibrosis (TA756)[65] assumed that utility for patients on "supportive care" (the last 30% of time on BAT) would fall every 24 weeks.
Transition to palliative care	Patient stops the current treatment and enters palliative care health state.	For a patient on fedratinib, remaining life expectancy is assessed at the TTD. If there are ≤ 8 weeks of remaining life expectancy, they will move to palliative care. In the final 8 weeks of life from the BAT state, a proportion of patients are moved to palliative care.	Clinical assumptions based on the premise that not all patients will receive palliative care, given that death is not always predictable.

BAT = best available therapy; JAK = Janus kinase; OS = overall survival; TTD = time to treatment discontinuation.

B.3.2.2.4 Model features

Key health economic outputs in line with NICE's reference case are included in the model. These include discounted and undiscounted costs, life-years (LYs), and QALYs as totals and as values that are disaggregated by health state. Costs are also presented by component (e.g., costs for drug acquisition, administration, resource utilisation, and AEs).

To assess cost-effectiveness, pairwise incremental cost-effectiveness ratios (ICERs) are presented. Additionally, incremental net monetary benefit, with a user-amendable willingness-to-pay (WTP) threshold, is also calculated by the model.

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The model has been developed from the perspective of the NHS and, as such, only considers direct costs in the base case.

Because the model outcomes focus on survival, a lifetime horizon was adopted. In the base case, the model considers a 30-year time horizon based on the median age in FREEDOM-2 of 69.3 years old. Shorter time horizons can be explored on scenario analysis.

In the base case, the model considers a 3.5% discount rate for costs and health effects in line with the NICE methods guide.[66]

Table 40 presents features of the economic analysis.

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Table 40. Features of the economic analysis

	Previous evaluations		Current evaluation	
Factor	**TA386**	**TA756**	**Chosen values**	**Justification**
Time horizon	Lifetime time horizon (30 years)	Lifetime time horizon (30 years)	Lifetime time horizon (30 years)	The reference case stipulates that the time horizon should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Therefore, a lifetime time horizon is considered sufficient to capture all meaningful differences.
Treatment waning effect?	None	The implementation of *duration of response* within the model acts as a waning treatment effect, in that response is not artificially maintained for the entire treatment duration.	The implementation of *duration of response* within the model acts as a waning of treatment effect, in that response is not artificially maintained for the entire treatment duration.	This reflects the clinical data to represent a more accurate portrayal of the disease. In a discrete-event simulation model, which uses a time-to-event framework, traditional hazards adjustment for treatment effect waning cannot be performed given there are no time cycles over which to do so. The same duration of response is used for both arms, which may be a conservative assumption given that a greater proportion of patients respond to fedratinib, which may indicate deeper/longer response.
Source of utilities	A condition-specific preference-based measure for myelofibrosis (MF-8D) was developed and applied to COMFORT-I data.	Treatment health-state utilities were estimated using the MF-8D in JAKARTA-2. Other health-state utilities (AML and palliative care) were externally sourced, and both estimated using the EQ-5D.	Treatment health-state utilities were estimated using the MF-8D in FREEDOM-2. Other health-state utilities (AML and palliative care) were externally sourced, and both estimated using the EQ-5D (TA386 and TA756).	The NICE reference case stipulates that the EQ-5D is the preferred measure of health-related quality of life in adults. Some evidence suggests that the EQ-5D does not sufficiently capture HRQOL in myelofibrosis.[67] Therefore, the MF-

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Factor	Previous evaluations		Current evaluation	
	TA386	TA756	Chosen values	Justification
		A worsening utility decrement for BAT, applied in scenario analysis, was taken from TA386.	Health-state utilities are reported for responders and non-responders for JAK and BAT. AE data were taken from FREEDOM-2	8D, a condition-specific measure, was used where possible. Responders and non-responders' health-state utilities are applied to the corresponding patient group. Externally sourced utilities were used to appropriately estimate utilities that required longer-term data or greater sample size.
Source of costs	Resource use unit costs were sourced from NHS Reference Costs and PSSRU costs. The main source for AE costs was a previous appraisal of enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen (TA316), which primarily used NHS Reference Costs. Administration costs were not included. Drug acquisition costs were taken from the BNF.	Resource use and AE cost sources were consistent with those used in TA386, using updated values or inflating values to a 2019 cost year. Administration costs were taken primarily from NHS Reference Costs. Drug acquisition costs were taken primarily from MIMS. eMIT was used for drugs available in generic form.	Resource use and AE cost sources were consistent with those used in TA386 and TA756, using updated values or inflating values to a 2022 cost year. Administration costs were taken primarily from NHS Reference Costs. Drug acquisition costs were taken primarily from MIMS. eMIT was used for drugs available in generic form.	NHS Reference Costs, PSSRU, MIMS and eMIT are standard sources of UK-relevant costs and were used where possible. Where costs were not reported in these sources, cost inputs were sourced from appropriate literature.

AE = adverse event; AML = acute myeloid leukaemia; BAT = best available therapy; BNF = British National Formulary; eMIT = electronic market information tool; HRQOL = health-related quality of life; JAK = Janus kinase; MF-8D = Myelofibrosis 8 Dimensions; MIMS = Monthly Index of Medical Specialities; NHS = National Health Service; PSSRU = Personal Social Services Research Unit; UK = United Kingdom.

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B.3.2.3 Intervention technology and comparators

Fedratinib is an oral kinase inhibitor with activity against wild-type and mutationally activated JAK-2 and FMS-like tyrosine kinase 3 (FLT3). Fedratinib has a higher potency for JAK-2 over family members JAK-1, JAK-3, and tyrosine kinase 2 (TYK2). Abnormal activation of JAK-2 is associated with myeloproliferative neoplasms, including myelofibrosis and polycythaemia vera. Fedratinib has been compared with BAT in the FREEDOM-2 clinical trial, as presented in Section B.2.

In the cost-effectiveness model, the comparator of interest is BAT. The use of BAT as a comparator aligns current clinical practice, with the design of comparative clinical trials in myelofibrosis and previous ruxolitinib economic modelling. The composition of BAT from FREEDOM-2 is shown in Table 41. This table also shows how BAT changes in the model after fedratinib is discontinued to reflect a reduction in prescribing JAK inhibitors after discontinuation of both ruxolitinib and fedratinib. Of note, the proportion of patients receiving ruxolitinib in BAT was highlighted as an area of uncertainty in TA756; use of the observed proportion from FREEDOM-2 now resolves this uncertainty.

In the model, suboptimal fedratinib corresponds to fedratinib given in subsequent BAT treatment for patients who initially responded to fedratinib treatment. For the base case, it is assumed that suboptimal fedratinib does not occur (the rate is 0%). A scenario analysis explored suboptimal fedratinib given to 32.1% of responding patients receiving BAT. This was based on the discontinuation rate of fedratinib of 67.9% at the cutoff date.[36] It was assumed that these patients would not receive fedratinib, if fedratinib was to be considered as part of BAT. Therefore, it was assumed that all patients who had not discontinued fedratinib (32.1%) would continue fedratinib as part of BAT. This is a strong conservative assumption.

Table 41. FREEDOM-2: composition of BAT

Treatment	BAT (as comparator)	BAT (after fedratinib, responders)	BAT (after fedratinib, non-responders)
Danazol	1.5%	11.3%	16.7%
Hydroxycarbamide (hydroxyurea)	1.5%	11.3%	16.7%
Interferon alfa	1.5%	11.3%	16.7%
Prednisolone	1.5%	11.3%	16.7%
Prednisone	1.5%	11.3%	16.7%
Thalidomide	1.5%	11.3%	16.7%
Ruxolitinib	77.6%	0%	0%
Fedratinib	0%	32.1%	0%

BAT = best available therapy.

Source: BMS data on file[36]

B.3.3 Clinical parameters and variables

B.3.3.1 Response assessment

The key types of response in myelofibrosis are spleen response and symptom response. The myelofibrosis-related symptoms evaluation is performed using the MFSAF version 4.0 using a 7-day recall period. Response assessments are assumed to occur at the end of cycles 3, 6, 12, 18, and 24 (and at the end of every sixth cycle as applicable afterwards; assessment of spleen size by palpation

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and symptoms score only). Cycles are defined for administrative purposes as 4-week (28-day) periods irrespective of the assigned treatment arm.[36]

Spleen volume reduction and TSS are assessed at the end of the sixth cycle, which is equivalent to 24 weeks of treatment.

B.3.3.2 Spleen volume reduction response rate

A ≥ 35% SVR was used, considered by the IWG-MRT and European LeukemiaNet (ELN) as appropriate for response in patients with myelofibrosis.[52,68] Treatment with fedratinib is associated with a statistically significant improvement in spleen response rate ($P < 0.0001$), with 35.8% of patients achieving ≥ 35% SVR at the end of the sixth cycle in the fedratinib arm. This compares to an SVR response of 6.0% in the BAT arm.

The values presented in Table 42 were retrieved from the FREEDOM-2 clinical trial and included in the model for SVR response rates.

Table 42. FREEDOM-2: SVR response rates

	Responders (n)	Patients (N)	Responders (%)	Source
Fedratinib	48	134	35.8	FREEDOM, CSR Table 7.2.1-1
BAT	4	67	6.0	FREEDOM, CSR Table 7.2.1-1

BAT = best available therapy; CSR = clinical study report; SVR = spleen volume reduction.

Source: BMS data on file[36]

B.3.3.3 Total symptom score response rates

Treatment with fedratinib was associated with considerable symptom relief, with an improvement in TSS in 34.1% of patients in the fedratinib arm, whereas 16.9% of patients in the BAT arm achieved the clinically meaningful threshold for response of ≥ 50% reduction. This improvement was statistically significantly ($P < 0.0001$).

The values presented in Table 43 were retrieved from the FREEDOM-2 clinical trial and included in the model.

Table 43. FREEDOM-2: TSS response rates at EOC6

	Responders (n)	Patients (N)	Responders (%)	Source
Fedratinib	43	126	34.1	FREEDOM-2, CSR Table 7.3.1.1-1
BAT	11	65	16.9	FREEDOM-2, CSR Table 7.3.1.1-1

BAT = best available therapy; CSR = clinical study report; EOC = end of cycle; TSS = total symptom score.

Source: BMS data on file[36]

B.3.3.4 Spleen volume reduction or total symptom score response rates

Spleen or symptom response rate is defined as the number of patients achieving either ≥ 35% SVR or ≥ 50% reduction in TSS. A combined endpoint of spleen or symptom response was strongly recommended as a modelling input by experts at an advisory board, with the rationale that this outcome would be reflective of UK clinical practice given that the SVR and TSS track together.[23] The FREEDOM-2 clinical trial did not report such data directly. Consequently, SVR or TSS response rate was calculated using available data from the clinical study report.[36]

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The values presented in Table 44 are included in the model and demonstrate improved levels of response with fedratinib.

Table 44. SVR or TSS response rates calculated from FREEDOM-2

	Responders (n)	Patients (N)	Responders (%)	Source
Fedratinib	70	134	52.24	FREEDOM-2 analysis
BAT	13	67	19.40	FREEDOM-2 analysis

BAT = best available therapy; SVR = spleen volume reduction; TSS = total symptom score.

Source: BMS data on file[36]

B.3.3.5 Adverse events

Only non-haematological AEs grade ≥ 3 are explicitly modelled. The impacts of thrombocytopenia, anaemia, and neutropenia (common AEs in myelofibrosis) on costs and utilities are assumed to be captured elsewhere by the model. Costs of haematological AEs are considered by the "resource utilisation" of patients on either JAK inhibitors or BAT; and the impact on utilities of such AEs is assumed to be captured within the health-state utility values. Transformation to AML is also an important aspect of the progression and natural history of myelofibrosis, therefore, the economic model quantifies its impact by including AML as an AE. The model was set up to account for other "placeholder" AEs to facilitate updates in local adaptations.

Adverse event data were taken from FREEDOM-2 for both the fedratinib and BAT arm.[36] Adverse events were retrieved using the exposure-adjusted incidence rate per 100 person-years. The exposure-adjusted incidence rate was calculated by dividing the number of patients with specified TEAEs by the total exposure time (in years) to the event, and then dividing the result by 100. Exposure time was the TEAE follow-up time for patients without the event and the time up to the first event start date for patients with the event. The overall exposure time was 146.47 patient-years for the fedratinib group and 39.62 patient-years for the BAT group. This approach was used to obtain the AEs for the full treatment period rather than using the data for the first 6 treatment cycles, as longer follow-up makes more use of the available evidence, reducing uncertainty (by including more events). The reported data for the first 6 treatment cycles were also deemed to be less suitable as these data do not adjust for duration of exposure.

The exposure-adjusted incidence rate (per 100 people years) is then used in the model to calculate the annual incidence rate.

For AEs in BAT after fedratinib, the user has the option to choose between COMFORT-II or FREEDOM-2. FREEDOM-2 did not report AEs for BAT after fedratinib; however, no strong discrepancy is expected to be experienced by patients receiving BAT after fedratinib when compared with patient receiving BAT as the comparator treatment. Hence, the AE rates for BAT as the comparator were used for AE rates when receiving BAT after fedratinib.

The AEs from FREEDOM-2 and COMFORT-II are reported in Table 45 and Table 46, respectively.

There was no observed transformation to AML in FREEDOM-2. Nevertheless, this was included in the model AEs list to reflect the potentiality that myelofibrosis may also transform to AML. The incidence for transformation to AML was taken from the NICE 2016 TA386 Committee papers, used in TA756 as well[65], and included in the model.[10] Rates of transformation to AML were assumed to be the same for both fedratinib and BAT, consistent with the committee's preferred assumptions in TA756.

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Table 45. FREEDOM-2: grade 3+ adverse events experienced by participants

	Exposure-adjusted incidence rate Full treatment period		Annual incidence		
Adverse event	**Fedratinib**	**BAT**	**Fedratinib**	**BAT**	**Source**
Abdominal pain	1.37	2.57	0.0137	0.0257	FREEDOM-2 CSR, Table 8.6.3-1[36]
Acute kidney injury	6.32	2.53	0.0632	0.0253	FREEDOM-2 CSR, Table 8.6.3-1[36]
ALT increase	4.32	0.00	0.0432	0.00	FREEDOM-2 CSR, Table 8.6.3-1[36]
AST increase	1.38	0.00	0.0138	0.00	FREEDOM-2 CSR, Table 8.6.3-1[36]
Asthenia	2.80	2.53	0.0280	0.0253	FREEDOM-2 CSR, Table 8.6.3-1[36]
Atrial fibrillation	1.39	0.00	0.0139	0.00	FREEDOM-2 CSR, Table 8.6.3-1[36]
Cardiac congestive failure	2.05	0.00	0.0205	0.00	FREEDOM-2 CSR, Table 8.6.3-1[36]
Chronic kidney injury	3.48	0.00	0.0348	0.00	FREEDOM-2 CSR, Table 8.6.3-1[36]
Decreased appetite	2.77	2.53	0.0277	0.0253	FREEDOM-2 CSR, Table 8.6.3-1[36]
Diarrhoea	1.37	0.00	0.0137	0.00	FREEDOM-2 CSR, Table 8.6.3-1[36]
Dyspnoea	2.09	0.00	0.0209	0.00	FREEDOM-2 CSR, Table 8.6.3-1[36]
Emphysema	1.38	0.00	0.0138	0.00	FREEDOM-2 CSR, Table 8.6.3-1[36]
Gastrointestinal haemorrhage	1.37	0.00	0.0137	0.00	FREEDOM-2 CSR, Table 8.6.3-1[36]
General physical health deterioration	7.64	2.53	0.0764	0.0253	FREEDOM-2 CSR, Table 8.6.3-1[36]
Glomerular filtration rate decreased	2.10	0.00	0.0210	0.00	FREEDOM-2 CSR, Table 8.6.3-1[36]
Hyperkalaemia	8.00	0.00	0.0800	0.00	FREEDOM-2 CSR, Table 8.6.3-1[36]
Hypokalaemia	2.06	2.56	0.0206	0.0256	FREEDOM-2 CSR, Table 8.6.3-1[36]
Hyponatraemia	1.37	0.00	0.0137	0.00	FREEDOM-2 CSR, Table 8.6.3-1[36]
Pneumonia	2.10	7.62	0.0210	0.0762	FREEDOM-2 CSR, Table 8.6.3-1[36]
Renal failure	2.75	0.00	0.0275	0.00	FREEDOM-2 CSR, Table 8.6.3-1[36]
Renal impairment	2.11	0.00	0.0211	0.00	FREEDOM-2 CSR, Table 8.6.3-1[36]

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BAT = best available therapy; CSR = clinical study report.

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Table 46. COMFORT-II: grade 3+ adverse events experienced by participants

Adverse event	COMFORT-II n[a]	COMFORT-II N	COMFORT-II %	Annual incidence	Source
Abdominal pain	3	73	4.11	0.0447	Cervantes et al. (2013),[69] COMFORT-II, Table 2
Arthralgia	0	73	0.00	0.0000	Cervantes et al. (2013),[69] COMFORT-II, Table 2
Asthenia	1	73	1.37	0.0149	Cervantes et al. (2013),[69] COMFORT-II, Table 2
Back pain	0	73	0.00	0.0000	Cervantes et al. (2013),[69] COMFORT-II, Table 2
Bronchitis	1	73	1.37	0.0149	Cervantes et al. (2013),[69] COMFORT-II, Table 2
Cough	1	73	1.37	0.0149	Cervantes et al. (2013),[69] COMFORT-II, Table 2
Diarrhoea	0	73	0.00	0.0000	Cervantes et al. (2013),[69] COMFORT-II, Table 2
Dyspnoea	3	73	4.11	0.0447	Cervantes et al. (2013),[69] COMFORT-II, Table 2
Fatigue	0	73	0.00	0.0000	Cervantes et al. (2013),[69] COMFORT-II, Table 2
Headache	0	73	0.00	0.0000	Cervantes et al. (2013),[69] COMFORT-II, Table 2
Nausea	0	73	0.00	0.0000	Cervantes et al. (2013),[69] COMFORT-II, Table 2
Oedema peripheral	1	73	1.37	0.0149	Cervantes et al. (2013),[69] COMFORT-II, Table 2
Pain in extremity	0	73	0.00	0.0000	Cervantes et al. (2013),[69] COMFORT-II, Table 2
Pyrexia	0	73	0.00	0.0000	Cervantes et al. (2013),[69] COMFORT-II, Table 2
Weight increased	0	73	0.00	0.0000	Cervantes et al. (2013),[69] COMFORT-II, Table 2
Transformation to AML	4	73	5.48	0.287	NICE (2016),[10] TA386, Committee papers (ACD), COMFORT-II, Table 36

ACD = Appraisal Consultation Document; AML = acute myeloid leukaemia.

[a] Number of patients experiencing the adverse event.

B.3.3.6 Survival analyses

B.3.3.6.1 Overview of survival analyses conducted for the economic model

Patient-level data from FREEDOM-2 were used to fit standard parametric models for the following 2 time-to-event outcomes incorporated into the economic model:

- OS, defined as the time from trial start to death
- Time to treatment discontinuation (TTD), defined as the time from trial start to discontinuation of the study treatment

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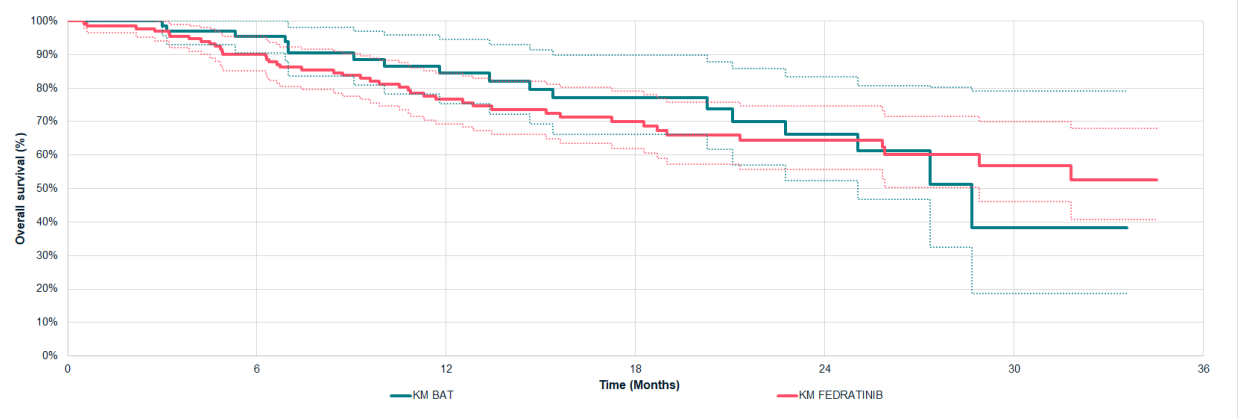
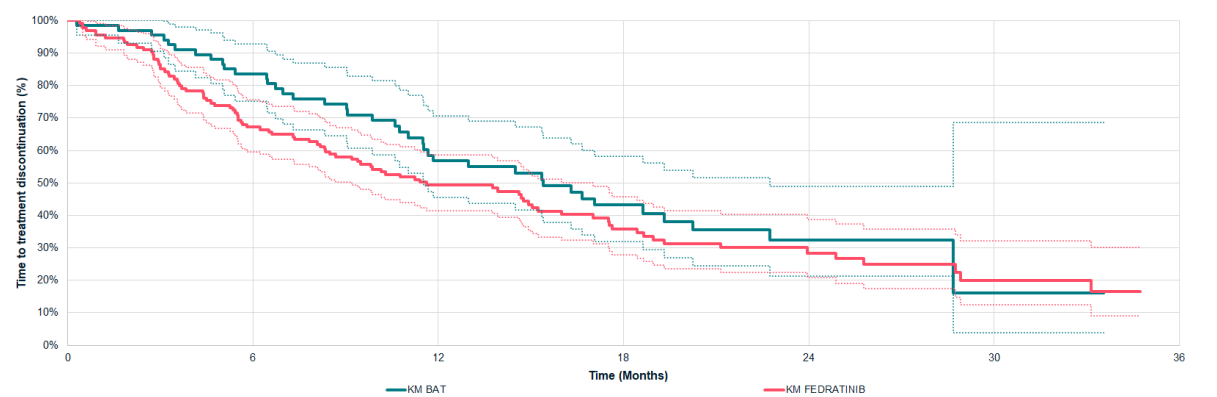
Graphs of OS and TTD by treatment (including CIs) are provided in Figure 37 and Figure 38.

Figure 37. Kaplan-Meier data for overall survival in fedratinib and BAT



BAT = best available therapy; KM = Kaplan-Meier.

Figure 38. Kaplan-Meier data for TTD in fedratinib and BAT



BAT = best available therapy; KM = Kaplan-Meier; TTD = time to treatment discontinuation.

For both outcomes, Figure 37 and Figure 38 show similar patterns, with little difference by treatment arm and crossing of curves towards the end of follow-up.

For OS, there is close alignment between the fedratinib and BAT curves, with a slight increase in OS for the fedratinib group at the end of follow-up. As presented in Section B.2, patients receiving BAT were eligible to cross over to fedratinib, either after confirmed progression of splenomegaly or after 24 weeks (6 cycles). This crossover does not represent the current or planned future treatment pathway for fedratinib, and so may be artificially inflating OS for the BAT arm compared with what would be observed in clinical practice. In addition, as shown in Section B.3.3.4, fedratinib is associated with statistically significant improvements in response when compared with BAT. This finding held for both response definitions (SVR and TSS). In several earlier studies, improved response rates have been found to be associated with improved survival.[70-73] Hence, it is plausible that the improved response rates observed with fedratinib may translate into improved long-term OS and thus indicate that the treatment effect of BAT in FREEDOM-2 could be overestimated.

As presented in Section B.2.6.1.6, crossover-adjustment methods were explored to formally investigate the impact of crossover on OS so that the effect of subsequent fedratinib in the BAT arm could be adjusted for. However, as presented in Section B.2.6.1.6, based on the observed OS results, a formal comparison of analyses was challenging, given the high risk of bias in the adjustment methods explored. Of importance, the underlying assumptions of the crossover-adjustment methods were likely

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violated. The trial characteristics (i.e., switching mechanism), data availability (i.e., small sample size, limited covariate inclusion feasibility), and trial results (i.e., difference in treatment arms with respect to prior anticancer therapies, observed OS estimates favour the control arm vs. the experimental arm) from FREEDOM-2 contributed to the violations of the underlying assumptions of these methods. As such, estimates obtained from the crossover-adjustment methods are not considered scientifically robust for decision-making. When applied to FREEDOM-2, the RPSFT, TSEsimp, and IPCW methods all provided contradictory results. Given the limitations, none of the crossover-adjustment methods therefore could be recommended for estimating OS in the economic model. Due to these limitations with the crossover-adjustment methods, as a conservative approach, it was assumed in the base case that there was no OS difference by treatment arm, with survival outcomes pooled across fedratinib and BAT. However, approaches for adjusting for a treatment-switching effect without using formal crossover-adjustment methods were considered to allow for scenario analyses to be conducted. First, an explicit association between response status and OS was modelled. Second, the effect of improved response on improved OS was implicitly modelled by extrapolating the observed treatment-specific outcomes (hence the improved response rates observed with fedratinib are reflected by the extrapolated OS which can be better than that for BAT). Third, OS for the BAT arm excluding patients who crossed over to receive fedratinib was modelled.

Outcomes for TTD were similar for the 2 treatment arms and hence were assumed to be equal in the base case. Similar to OS, outcomes for TTD may be influenced by both response status and crossover from BAT to fedratinib. Thus, the same set of analyses that were conducted for OS were also conducted for TTD.

Table 47 presents the different analyses used in the cost-effectiveness model. Of note, analyses considered 3 different definitions of response: SVR, TSS, and SVR or TSS. Only results for the last definition are provided in this report; results for the other 2 definitions were consistent with those presented.

Table 47. Survival analyses included in the model

Outcome	Treatment	Analysis	Rationale
OS	Fedratinib	Separate by responder status	Assess survival by endpoint for responders vs. non-responders (reflecting the known relationship between response and OS). Three endpoints were selected: SVR, TSS, and SVR or TSS. This is to understand the survival by each endpoint, by response. Both independent and dependent models were considered. For dependent models the covariate was response status.
		Pooled by responder status	Assess survival for fedratinib, regardless of the response status (implicitly capturing the impact of treatment-differences in response on outcomes). Three endpoints were selected: SVR, TSS, and SVR or TSS. This is to understand the survival magnitude by each endpoint, not split by response. Both independent and dependent models were considered. For dependent models the covariate was treatment arm.
	BAT	Separate by responder status	Assess survival by endpoint for responders vs. non-responders (reflecting the known relationship between response and OS). Three

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Outcome	Treatment	Analysis	Rationale
			endpoints were selected: SVR, TSS, and SVR or TSS. This is to understand the survival by each endpoint, by response. Both independent and dependent models were considered. For dependent models the covariate was response status. Note that there were no deaths in the BAT responder subgroup, so this analysis was only possible for the non-responders.
		Pooled by responder status	Assess survival by endpoint regardless of the response status (implicitly capturing the impact of treatment-differences in response on outcomes). Three endpoints were selected: SVR, TSS, and SVR or TSS. This is to understand the survival magnitude by each endpoint, not split by response. Both independent and dependent models were considered. For dependent models the covariate was treatment arm.
		Excluding patients who crossed over	Assess survival for patients in BAT arm who did not cross over, i.e., who stayed in the BAT arm and did not cross to fedratinib. This focused on the endpoint of SVR or TSS and was included to understand the true survival of the BAT arm.
	Pooled fedratinib/ BAT	Pooled between treatments fedratinib and BAT[a]	Assess survival for pooled fedratinib/BAT. This is to understand survival when OS is set equal for BAT and fedratinib and to avoid a model where the fedratinib OS curve is lower than the one of the BAT arm in the long-term. In this analysis, responders and non-responders are pooled as well. One endpoint (SVR or TSS) was considered.
TTD	Fedratinib	Separate by responder status	Assess TTD by endpoint for responders vs. non-responders (as response may influence TTD). Three endpoints were selected: SVR, TSS, and SVR or TSS. This is to understand the TTD by each endpoint, by response. Both independent and dependent models were considered. For dependent models, the covariate was response status.
		Pooled by responder status	Assess TTD for fedratinib, regardless of the response status (implicitly capturing the impact of treatment-differences in response on outcomes). Three endpoints were selected: SVR, TSS, and SVR or TSS. This is to understand the TTD by each endpoint, not split by response. Both independent and dependent models were considered. For dependent models, the covariate was treatment arm.
	BAT	Separate by responder status	Assess TTD by endpoint for responders vs. non-responders (as response may influence TTD). Three endpoints were selected: SVR, TSS, and SVR or TSS. This is to understand the TTD by each endpoint, by response. Both independent

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Outcome	Treatment	Analysis	Rationale
			and dependent models were considered. For dependent models the covariate was response status.
		Pooled by responder status	Assess TTD for BAT, regardless of the response status (implicitly capturing the impact of treatment-differences in response on outcomes). Three endpoints were selected: SVR, TSS, and SVR or TSS. This is to understand the TTD by each endpoint, not split by response. Both independent and dependent models were considered. For dependent models, the covariate was treatment arm.
		Excluding patients who crossed over	Assess TTD for patients in BAT arm who did not cross over, i.e., who stayed in the BAT arm and did not cross to fedratinib. This focused on the endpoint of SVR or TSS and was included to understand the true survival of the BAT arm.
	Pooled fedratinib/ BAT	Pooled between treatments fedratinib and BAT[a]	Assess TTD for pooled fedratinib/BAT. This is to understand treatment discontinuation when TTD is set equal for both arms. This analysis is consistent with the corresponding OS analysis and reflects the similarity of observed TTD outcomes. In this analysis, responders and non-responders are pooled as well. One endpoint (SVR or TSS) was considered.

BAT = best available therapy; OS = overall survival; SVR = spleen volume reduction; TSS = total symptom score; TTD = time to treatment discontinuation.

[a] Base-case setting.

To summarise, several endpoints were presented in the FREEDOM-2 clinical trial (SVR and TSS, separately or combined). Survival analyses were undertaken for these 3 endpoints for OS and TTD and were further subdivided by responders and the non-responders. These survival analyses were done both for the fedratinib and the BAT data, with the caveat that there were no deaths for responders in the OS BAT arm for any response definition (SVR, TSS, and SVR or TSS), so OS analyses were not possible for this subgroup. Hence, for the responder-based analyses, for OS there were 6 analyses for fedratinib and 3 for BAT. For TTD there were 6 analyses for fedratinib and 6 analyses for BAT: 2 analyses (responder and non-responder analysis) for each of the 3 endpoints.

Further analyses were then undertaken to pool responders and non-responders in each arm (i.e., there is no differentiation between responders and non-responders in the analysis). This is referred to in the model as *separated by treatment only*. This analysis has been undertaken for OS and TTD, and for both fedratinib and BAT. This results in 3 analyses (1 for each endpoint) for fedratinib and 3 analyses for BAT.

Two other analyses were undertaken, whereby fedratinib and BAT would be pooled together, meaning there would be no effective difference between the 2 treatments. This has been done for OS and TTD (for the endpoint of SVR or TSS), resulting in 2 analyses.

Finally, to account for patients crossing over from the BAT arm to the fedratinib arm, 2 analyses (1 each for OS and TTD) were performed to generate extrapolations for the BAT patients who did not cross over.

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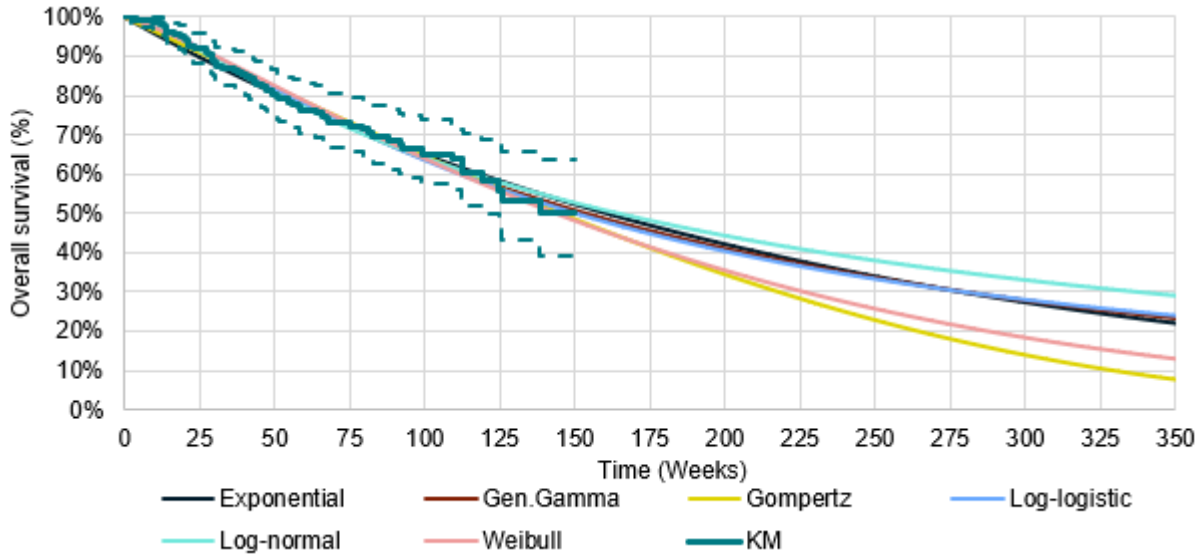
B.3.3.6.2 Overall survival

Time to death in the model is estimated using parametric survival curves. Parametric survival curves were estimated based on patient-level data, and the model accommodates inputs for 6 standard survival distributions (exponential, generalised gamma, Gompertz, log-logistic, log-normal, and Weibull), which are in line with NICE Decision Support Unit (DSU) Technical Support Document 14.[74]

In the base case, given that data shows no meaningful difference between fedratinib and BAT arms, the option to pool fedratinib and BAT together has been chosen to ensure that the OS survival function for BAT did not cross the OS survival function for fedratinib, which was deemed implausible by clinical experts consulted during an advisory board.[23] The clinicians said that it was not expected that the survival of BAT patients would exceed that of fedratinib patients at any point. An alternative scenario was also made available to choose a BAT OS survival function that would exclude the patients who did cross over to fedratinib.

For the base case, parametric curves were fit to fedratinib/BAT OS data in FREEDOM-2 (Figure 39), with the resulting estimates provided in Table 48. The log-logistic distribution was one of the best-fitting distributions, based on both the Akaike information criterion (AIC)/Bayesian information criterion (BIC) (Table 49) and on visual inspection. However, this predicts a 20-year survival rate of 7%. Clinical advice was that all patients were likely to be dead within 20 years. This suggests that the log-logistic is likely to overestimate long-term survival, along with the log-normal and generalised gamma. Visually, all models provide similar fit to the observed data. Of the plausible models, the Weibull and exponential distributions have the best fit based on the AIC and BIC, respectively. The exponential distribution assumes constant hazards at all timepoints. The plausibility of this assumption is questionable because hazards may be expected to increase in the long-term because of ageing. As such, the Weibull was chosen as the base-case distribution.

Figure 39. Overall survival pooled fedratinib/BAT



BAT = best available therapy; KM = Kaplan-Meier.

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Table 48. Observed and modelled estimates of survival over time

Time (years)	0	1	2	5	10	20
Number at risk	201	120	50	-	-	-
Kaplan-Meier	100%	79%	65%	-	-	-
Modelled survival over time						
Exponential	100%	80%	64%	32%	10%	1%
Generalised gamma	100%	81%	63%	32%	13%	4%
Gompertz	100%	81%	63%	21%	0%	0%
Log-logistic	100%	81%	62%	32%	15%	7%
Log-normal	100%	80%	63%	37%	20%	9%
Weibull	100%	82%	62%	24%	4%	0%

Table 49. AIC/BIC for overall survival: pooled fedratinib/BAT

Model	AIC	AIC rank	BIC	BIC rank
Exponential	799.06	6	791.36	1
Generalised gamma	787.95	4	797.86	6
Gompertz	789.05	5	795.65	5
Log-logistic	786.39	1	792.99	2
Log-normal	786.53	2	793.14	3
Weibull	787.24	3	793.85	4

AIC = Akaike information criterion; BAT = best available therapy; BIC = Bayesian information criterion.

Note: The lower the AIC/BIC value, the better it is suited to the data. All the distributions, except generalised gamma and Gompertz using the BIC, are within 5 points of the best-fitting model.

Appendix M presents details on the additional OS analyses and their implications for use in the model.

B.3.3.6.3 Time to treatment discontinuation

Time to treatment discontinuation in the model is estimated using parametric survival curves fit to the observed KM data; the model accommodates inputs for 6 standard survival distributions (exponential, generalised gamma, Gompertz, log-logistic, log-normal, and Weibull), in line with NICE DSU Technical Support Document 14.[74]

To maintain sample size and statistical robustness, pooled TTD curves are used in the base case. This reflects the similar outcomes observed in Figure 38 and is also consistent with the base-case approach to OS, which is to assume no difference by treatment and use pooled data. In addition, for the reasons previously detailed, the model also includes the option to split TTD by either treatment arm, or treatment arm and responder status. When this is selected, separate parametric curves are fit to the TTD KM data by arm, and if relevant, also for responders and non-responders; the option to select what response assessment is used is also provided (i.e., spleen, symptom, or spleen and symptom response).

A stopping rule can also be implemented in the model such that non-responders discontinue immediately at 24 weeks. When TTD is split by response status, this allows the stopping rule to be applied more accurately (i.e., TTD equals 0 from 24 weeks for the non-responder curve only). This stopping rule has been made available in the model after the advisory board meeting where it was stated that, in clinical practice, a stopping rule would be used if patients had not responded at week 24.

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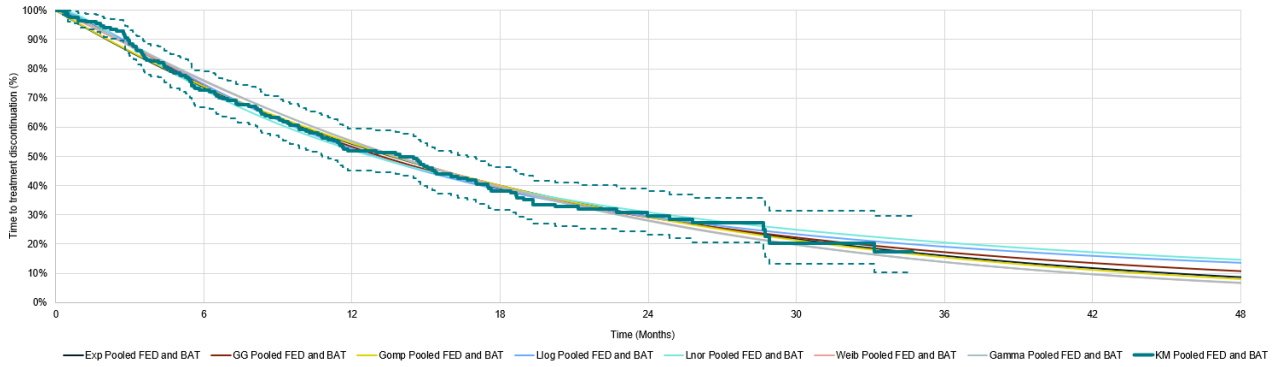
In the base case, the pooled fedratinib/BAT TTD option has been chosen, which means that TTD for fedratinib and BAT will be equal. This option means there is no differentiation in terms of treatment or in terms of responder status because all the data are pooled.

Parametric curves were fit to fedratinib/BAT TTD data in FREEDOM-2 (Figure 40). The log-logistic distribution was one of the best-fitting distributions, based on both the AIC/BIC tables (Table 50) and visual inspection, and therefore was chosen as the base-case distribution.

Figure 40. TTD pooled fedratinib/BAT



BAT = best available therapy; FED = fedratinib; GG = generalised gamma; KM = Kaplan-Meier; TTD = time to treatment discontinuation.

Table 50. AIC/BIC for TTD: pooled fedratinib/BAT

Model	AIC	AIC rank	BIC	BIC rank
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]

AIC = Akaike information criterion; BAT = best available therapy; BIC = Bayesian information criterion; TTD = time to treatment discontinuation.

Note: The lower the AIC/BIC value, the better it is suited to the data. All the distributions, except generalised gamma and Gompertz using the BIC, are within 5 points of the best-fitting model.

An alternative to the base case is to set the TTD for both the BAT responders and non-responders to use the FREEDOM-2 data for patients who did not cross over from the BAT arm to the fedratinib arm. This analysis allows the user to use parametric curves which do not contain patients who crossed over after progression or after cycle 6, giving a better idea of an unbiased TTD curve. As a reminder, in FREEDOM-2 clinical trial, patients are allowed to cross over from BAT to the fedratinib arm after the cycle 6 response assessment or before the cycle 6 response assessment in the event of a confirmed progression of splenomegaly by MRI/CT scan.

Parametric curves were fit to the BAT TTD data for patients who did not cross over from the FREEDOM-2 clinical trial (Figure 41). Table 51 presents the AIC and BIC values of the parametric distribution. Similar to the pooled fedratinib/BAT, the log-logistic distribution is among the lowest AIC/BIC, with a good fit to the KM data, and therefore was chosen as the base-case distribution for the alternative base case using TTD data for patients who did not cross over.

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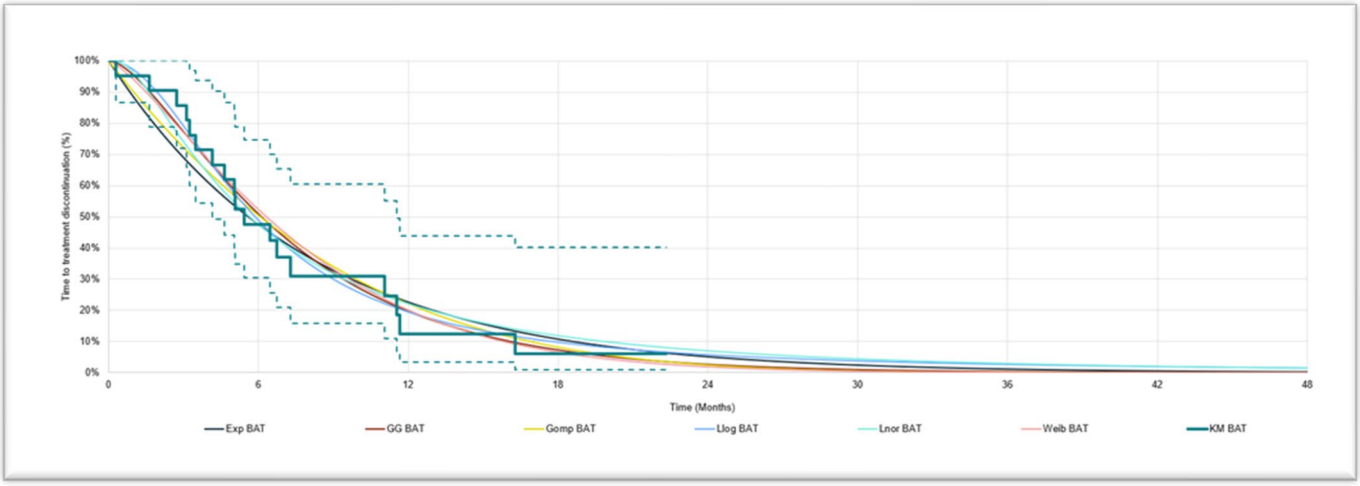
Figure 41. TTD for BAT for patients who did not cross over



BAT = best available therapy; GG = generalised gamma; KM = Kaplan-Meier; TTD = time to treatment discontinuation.

Table 51. AIC/BIC for TTD: BAT for patients who did not cross over

Model	AIC	AIC rank	BIC	BIC rank
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]

AIC = Akaike information criterion; BAT = best available therapy; BIC = Bayesian information criterion; TTD = time to treatment discontinuation.

Note: The lower the AIC/BIC value, the better it is suited to the data. All the distributions, except generalised gamma and Gompertz using the BIC, are within 5 points of the best-fitting model.

Appendix M presents details on the additional TTD analyses and their implications for use in the model.

B.3.3.7 Discontinuation after crossover to fedratinib

As previously noted, patients in the BAT arm could cross over to fedratinib. It is plausible that if these patients had not crossed over, they would have remained on BAT instead. No formal statistical adjustment for the effects of crossover on TTD was performed. Instead, an exploratory analysis of TTD after crossover to fedratinib was conducted. This analysis provides more insight into the comparison of TTD between treatment arms; it is not used within the economic model.

Evidence was available for 46 patients who crossed over from the BAT arm to fedratinib. Of the 46 patients, 21 experienced a treatment discontinuation event after crossing to fedratinib. For the 25 patients who did not discontinue treatment on fedratinib, their discontinuation date was set to be the study end date, and these patients were censored. Table 52 presents a naive summary of these patients (no adjustments for censoring). (Note: adjustment for censoring skews the median time on fedratinib to approximately [redacted] (CSR Table 14.3.1.1.1.1).

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Table 52. Treatment duration for patients who crossed over to fedratinib

N = 46	Mean (SD)	Median
Time on BAT (days)	[redacted]	[redacted]
Time on fedratinib (days)	[redacted]	[redacted]

BAT = best available therapy; SD = standard deviation

These results are provided as information only and are not incorporated within the cost-effectiveness model.

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

Health state utility values are assigned to the following health states:

- In treatment health states
  - Response
  - Non-response
- In end-of-life health states
  - Supportive care

In treatment health states, utility values that depend on response status are implemented as a change from baseline. The change in utility is assumed to start after 4 weeks of treatment, in line with the assumptions applied in the ruxolitinib NICE submission.[10] In the base case, consistent utility values for response and non-response are used between JAK inhibitors and BAT. In the ruxolitinib model (TA386[10]), a supportive care health state was included, which was associated with a decrement in utility every 24 weeks. Baseline utility and the utility values that depend on response status are informed by analyses of FREEDOM-2 data, described in more detail below.

Several secondary PRO endpoints were collected in FREEDOM-2. In particular, quality-of-life (QOL) measures were collected, such as EQ-5D-5L, MFSAF v4.0, and EORTC QLQ-C30. The Myelofibrosis 8 Dimensions (MF-8D) was considered the most appropriate QOL measure for this utility analysis because it was developed specifically in people with myelofibrosis.[67] This means that the MF-8D is more sensitive to changes in the QOL of people with myelofibrosis because the MF-8D is better able to estimate QOL of people with myelofibrosis compared with other instruments such as the EQ-5D. The MF-8D was also the QOL measure used in the original cost-effectiveness model for the fedratinib NICE TA756 submission.[75]

B.3.4.1.1 Utility regression in the model

The cost-effectiveness model uses a regression model to calculate the health utilities based on the increment in health utilities for responders and non-responders for both fedratinib and BAT; these estimates are added to the baseline health utilities for those aforementioned treatments. The regression model aims to produce health utilities with as few covariates (i.e., explanatory variables such as baseline health utility, response status, age, sex, and ECOG PS, among others) as possible. As a result, and considering the model allows for the exclusion or inclusion of gender, 2 models (treatment response, as well as treatment response + gender) were produced for each of the 3 response definitions (spleen response, symptom response, and spleen or symptom response). Regression output for FREEDOM-2 utilities is shown in Table 53.

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Table 53. FREEDOM-2: coefficients from the final regression model for each response definition using the MF-8D

Coefficient	Coefficient subcategory	Estimate	Standard error	*P* value
Spleen or symptom response model				
Intercept	NA	0.371	0.031	< 0.001
Baseline MF-8D utility	NA	0.509	0.043	< 0.001
Response status	Non-responder		Reference	
	Spleen or symptom responder	0.115	0.018	< 0.001
Spleen response model				
Intercept	NA	0.396	0.032	< 0.001
Baseline MF-8D utility	NA	0.518	0.046	< 0.001
Response status	Non-responder		Reference	
	Spleen responder	0.072	0.022	< 0.001
Symptom response model				
Intercept	NA	0.383	0.030	< 0.001
Baseline MF-8D utility	NA	0.509	0.042	< 0.001
Response status	Non-responder		Reference	
	Symptom responder	0.135	0.020	< 0.001

MF-8D = Myelofibrosis 8 Dimensions; NA = not applicable.

B.3.4.1.2 Utility results

The baseline health utilities included in the model do not include crossover observations because the definition for baseline for crossover patients was different than the one for patients who did not cross over. The baseline for crossover patients was defined as the last observation before crossover while patients were receiving BAT. The results are presented in Table 54.

Table 54. FREEDOM-2: summary of MF-8D baseline utility excluding crossover patients

Type	Observations	Patients	Mean (SD)	Median (range)
Baseline (all)[a]	155	155	0.649 (0.217)	0.662 (0.134-0.993)
Baseline (male)	82	82	0.711 (0.196)	NR
Baseline (female)	73	73	0.579 (0.220)	NR

MF-8D = Myelofibrosis 8 Dimensions; NR = not reported; SD = standard deviation.

[a] Out all the patients in FREEDOM-2, 34 patients had their baseline utility value imputed.

Table 54 displays utility at baseline for males, females, and all patients. The pooled baseline (all) is a weighted average of the baseline utility for males and females.

Regarding the increment in health utility associated with response, the results from the regression model indicate:

- Spleen or symptom response is associated with a 0.115 utility increment ($P < 0.001$)
- Spleen response is associated with a 0.072 utility increment ($P < 0.001$)
- Symptom response is associated with a 0.135 utility increment ($P < 0.001$)

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Table 55 presents estimated MF-8D utilities per response status based on a baseline utility value of 0.649. Results indicate that non-responders have an MF-8D utility value of approximately 0.7, which increases to 0.816 for spleen or symptom response, 0.804 for spleen response, and 0.848 for symptom response.

Table 55. Estimated MF-8D utilities from the final regression model for each response definition

	Estimated utility based on a baseline utility of 0.649 (from FREEDOM-2 data)		
Response status	**Spleen or symptom response**	**Spleen response**	**Symptom response**
Non-responder	0.701	0.732	0.713
Responder	0.817	0.805	0.848

MF-8D = Myelofibrosis 8 Dimensions.

Notes: Baseline utility has been assumed to be 0.649, based on the 155 patients in FREEDOM-2 who had baseline observations for MF-8D.

The model does not consider difference in gender and pools health utilities between male and female patients. Table 56 summarises health utility regression values and Table 57 the resulting utility values used in the model.

Table 56. Utility regression values by gender and health state

Utilities	Implementation	Female	Male	Source
Baseline	Baseline value	0.649	0.649	FREEDOM-2 analysis
JAK response	Change from baseline, after 4 weeks in state	+0.168	+0.168	FREEDOM-2 analysis
JAK non-response	Change from baseline, after 4 weeks in state	+0.052	+0.052	FREEDOM-2 analysis
BAT response	Change from baseline, after 4 weeks in state	+0.168	+0.168	FREEDOM-2 analysis
BAT non-response	Change from baseline, after 4 weeks in state	0.000	0.000	FREEDOM-2 analysis
Worsening utility	Ongoing 24-weekly decrement in supportive care	−0.025	−0.025	Ruxolitinib SMC detailed advice document

BAT = best available therapy; JAK = Janus kinase; SMC = Scottish Medicine Consortium.

Notes: Utilities for male and female patients are the same because they are pooled in the model. BAT non-responders are not experiencing any utility increment because this setting is turned off in the base case. If the setting is turned on, the increment is +0.052.

Table 57. Utility values by gender and health state

Utilities	Pooled	Source
Non-responder (FED)	0.701	FREEDOM-2 analysis
Non-responder (BAT)	0.649	FREEDOM-2 analysis
Responder (FED)	0.817	FREEDOM-2 analysis
Responder (BAT)	0.817	FREEDOM-2 analysis

BAT = best available therapy; FED = fedratinib.

Note: This health utility values are for spleen or symptom response.

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B.3.4.1.3 Utility decrement in supportive care

In the cost-effectiveness model, an ongoing 24-weekly utility decrement for patients in supportive care of −0.025 was applied equally between patient arms. This utility value has been included in the model to reflect a worsening QOL over time due to the disease; the utility value is also independent of age-related utility decline and is the value used previously. An analysis of FREEDOM-2 data was performed to explore the feasibility of updating this value using utility estimates from 30-day posttreatment discontinuation (pooled across responders and non-responders). Evidence was only available from 24 patients, with inconclusive results: mean change −0.014 (SD, 0.148), median change +0.04 (range, −0.245 to 0.351). Hence, this additional information was not incorporated within the model. As a further exploratory analysis, the change in utility from baseline to week 8 for non-responders (excluding patients who crossed over) was also estimated. The rationale for this was that non-response may be viewed as a proxy for treatment not working, so HRQOL may be similar to people who are off treatment. This demonstrated a marginal increase in utility: mean change +0.056 (SD, 0.170), median change +0.08 (range, −0.235 to 0.668). Hence, this additional information was also not incorporated within the model.

A switch is included in the model to let the user decide whether to include or exclude the utility decrement in the analysis.

B.3.4.1.4 Age-related utility adjustment

To account for the natural decline in QOL over time, utilities in the model can be adjusted throughout based on the patient's age. The adjustment is based on a formula published by Alava et al.[76] Alava et al. used data from the latest available wave of the Health and Safety Executive that includes the EQ-5D-3L, which was published in 2014. A total of 8,077 individuals aged 16 years and older were included in the database. The authors estimated adjusted limited-dependent variable mixture models separately for male and female patients to allow for different EQ-5D-3L age profiles.

In the cost-effectiveness model, the user can choose between the Alava et al.[76] or the Ara and Brazier[77] algorithm in the model. The Ara and Brazier article uses a different population (26,679 observations pooled across years 2003-2006) and is less up to date than the Alava article.

In the model, age-specific utility values are predicted for male and female patients, starting from the baseline age up to the end of the time horizon (a maximum of 40 years). Age-specific utility multipliers are derived by reweighting the utility values relative to the baseline age. The multipliers are then applied in the model patient flow sheets when calculating QALYs.

B.3.4.2 Mapping

Generic preference-based measures of health, such as the EQ-5D, can be used to support the analysis of utility gains from treatments. In the absence of EQ-5D data, mapping algorithms are often used to link the outcomes from alternative measures of HRQOL to EQ-5D, or other generic preference-based measures. Because EQ-5D data are available from FREEDOM-2, no mapping has been necessary.

There are some concerns regarding the ability of the generic EQ-5D to detect clinically meaningful changes in the HRQOL of people with myelofibrosis.[67] This includes the exclusion of relevant symptoms such as nausea and vomiting.[67]

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B.3.4.3 Health-related quality-of-life studies

Appendix H presents full details of the systematic searches conducted to identify relevant HRQOL data. The SLR was supplemented by targeted searches to identify utility estimates specific to AML and palliative care health states.

B.3.4.4 Adverse reactions

The impacts of thrombocytopenia, anaemia, and neutropenia on costs and utilities are assumed to already be captured by the model; therefore, disutilities for these are not included in the base case. Disutility values have been identified from the literature and are reported in Table 58.

For transformation to AML events, the assumed disutility was derived by back calculating the AML QALY decrement reported in NICE TA386 and TA756. The assumed duration of AML was also derived from TA386; this was 3.9 months.

For all other modelled AEs, in the absence of data on the duration, a length of 4 weeks was assumed for disutility calculations.

Table 58. Adverse event disutilities

Adverse event	Disutility	Source
Abdominal pain	0.11	Tielemans et al. (2013),[78] disutility for "gastrointestinal symptoms"
Acute kidney injury	0	Assumption, no source identified
ALT increase	0.15	NICE TA677[79]; Committee Papers, p. 149/606
AST increase	0.15	NICE TA677[79]; Committee Papers, p. 149/606
Asthenia	0.09	Beusterien et al. (2010),[80] disutility of grade 3-4 anaemia
Atrial fibrillation	0.047	Schremser et al. (2015),[81] advanced lung adenocarcinoma patients
Cardiac congestive failure	0	Assumption. No sources identified.
Chronic kidney injury	0	Assumption. No sources identified.
Decreased appetite	0.038	[ID1182] Disutility for decreased weight grade 3+ from TA498[82]
Diarrhoea	0.047	Schremser et al. (2015),[81] advanced lung adenocarcinoma patients
Dyspnoea	0.219	Lachaine et al. (2015),[83] in relapsed acute promyelocytic leukaemia
Emphysema	0.219	Lachaine et al. (2015),[83] in relapsed acute promyelocytic leukaemia
Gastrointestinal haemorrhage	0.038	[ID1182] Disutility for decreased weight grade 3+ from TA498[82]
General physical health deterioration	0.22	Assumed equal to arthralgia
Glomerular filtration rate decreased	0.09	Nafees et al. (2008),[84] in non–small cell lung cancer
Hyperkalaemia	0.012	Matza et al. (2019)[85]
Hypokalaemia	0.012	Matza et al. (2019)[85]
Hyponatraemia	0.012	Matza et al. (2019)[85]
Pneumonia	0.012	Matza et al. (2019)[85]
Renal failure	0.15	NICE TA677[79]; Committee Papers, p. 149/606
Renal impairment	0.15	NICE TA677[79]; Committee Papers, p. 149/606
Transformation to AML	0.462	Back calculation from TA386[10]

ALT = alanine aminotransferase; AML = acute myeloid leukaemia; AST = aspartate aminotransferase.

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B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

Patients are assigned a baseline utility value in the model that is consistent between the intervention and the comparator. The HRQOL data that were used in the cost-effectiveness analysis are presented in Table 59 and include the following health states: treatment response, treatment non-response, loss of response to treatment, AML, and palliative care.

Table 59. Summary of utility values for cost-effectiveness analysis

State		Utility value: mean (standard error)	95% CI	Reference in submission (section and page number)	Justification
Baseline (all)	Baseline utility for the first 4 weeks after patient first receives treatment	0.649 (0.217)	NA	Section 3.4 (p. 109, Table 56)	Derived from MF-8D FREEDOM-2 analysis
JAK treatment response (both male and female)	Change from baseline after 4 weeks in state	+0.168	(0.1669-0.1684)	Section 3.4 (p. 109,Table 56)	Derived from MF-8D FREEDOM-2 analysis
JAK -non-response (both male and female)	Change from baseline after 4 weeks in state	+0.052	(0.0199-0.0847)	Section 3.4 (p. 109,Table 56)	Derived from MF-8D FREEDOM-2 analysis
BAT response (both male and female)	Change from baseline after 4 weeks in state	+0.168	(0.1669-0.1684)	Section 3.4 (p. 109,Table 56)	Derived from MF-8D FREEDOM-2 analysis
BAT non-response (both male and female)	Change from baseline after 4 weeks in state	0.000	NA	Section 3.4 (p. 109,Table 56)	Derived from MF-8D FREEDOM-2 analysis
Worsening utility (both male and female)	Ongoing 24 weekly decrement in supportive care	−0.025	NA	Section 3.4 (p. 109,Table 56)	Ruxolitinib SMC detailed advice document
AML	Utility value for patients who transition to AML health state	0.462	NA	Section 3.4.4 (p. 111,Table 58)	Back calculation from TA386

AML = acute myeloid leukaemia; BAT = best available therapy; CI = confidence interval; JAK = Janus kinase; MF-8D = Myelofibrosis 8 Dimensions; NA = not available; SMC = Scottish Medicines Consortium.

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B.3.5 Cost and healthcare resource use identification, measurement, and valuation

An SLR was conducted to identify any relevant cost and healthcare resource use data associated with the treatment of patients with myelofibrosis. Appendix I outlines the methods used in the SLR.

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Acquisition costs

Total drug acquisition costs are calculated for all patients remaining alive in each arm of the model, based on label dosing regimens and list prices. The composition of BAT, based on the FREEDOM-2 clinical trial, is available in Table 41 in Section B.3.2.3.

Drug acquisition costs were sourced primarily from the Monthly Index of Medical Specialities (MIMS) online database.[86] For drugs available in generic form, acquisition costs were sourced from the drugs and pharmaceutical electronic market information tool (eMIT) because eMIT costs are based on actual purchases made by the NHS as opposed to list prices.[87] Where multiple costs were identified for treatments in BAT, the cost was selected based on the lowest cost per milligram, as long as the strength was a valid option for the dose.

Wastage is also included in the model to account for frequent dose adjustments on ruxolitinib, which results in the remaining tablets within a pack being discarded. In the base-case analysis wastage is directly incorporated in the estimation of the number of packs of ruxolitinib required per cycle (as it incorporates dose changes). An alternative approach to calculating the number packs of ruxolitinib required per cycle uses information on the mean initial dose, which does not include wastage. For this scenario, a 5% rate of wastage can be included as an option as per the initial EAG preference. The acquisition costs used in the model are presented in Table 60 for the oral and intravenous therapies. Of note, only interferon-alpha is currently used in the model base case.

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Table 60. Drug acquisition unit costs (oral therapies)

Treatment	Pack size	Unit size	Unit type	Pack cost (£)	Cost per unit (£)	Reference
Fedratinib	120	100	Tablet	[redacted]	[redacted]	BMS
Anagrelide	100	0.5	Tablet	404.57	4.05	MIMS 2023[88]
Busulfan	8	6	Solution for infusion	169.18	21.15	eMIT[87]
Danazol	30	200	Capsule	97.64	3.25	eMIT[87]
Hydroxycarbamide (hydroxyurea)	100	500	Capsule	10.00	0.10	eMIT[87]
Prednisolone	28	1	Tablet	0.20	0.007	eMIT[87]
Prednisolone	28	2.5	Tablet (gastro resistant)	0.64	0.023	eMIT[87]
Prednisolone	30	2.5	Tablet (gastro resistant)	0.64	0.021	eMIT[87]
Prednisolone	56	25	Tablet	12.41	0.222	eMIT[87]
Prednisolone	28	5	Tablet (gastro resistant)	1.23	0.044	eMIT[87]
Prednisolone	30	5	Tablet (soluble)	7.83	0.261	eMIT[87]
Prednisolone	28	5	Tablet	0.30	0.011	eMIT[87]
Prednisone	28	1	Tablet	0.77	0.0275	BNF[89]
Prednisone	28	2	Tablet	10.2	0.364	BNF[89]
Prednisone	28	5	Tablet	0.94	0.034	BNF[89]
Thalidomide	28	50	Capsule	298.48	10.66	MIMS 2023[90]
Ruxolitinib (5 mg)	56	5	Tablet	1,428	25.5	MIMS 2023[91]
Ruxolitinib (10 mg)	56	10	Tablet	2,856	51	MIMS 2023[91]
Ruxolitinib (15 mg)	56	15	Tablet	2,856	51	MIMS 2023[91]
Ruxolitinib (20 mg)	56	20	Tablet	2,856	51	MIMS 2023[91]
Cytarabine	5	20	Solution for vial	20.48	0.041	MIMS 2023[88]
Cytarabine	5	100	Solution for vial	26.93	0.054	MIMS 2023[88]

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Treatment	Pack size	Unit size	Unit type	Pack cost (£)	Cost per unit (£)	Reference
Cytarabine	1	100	Solution for vial	37.05	0.037	MIMS 2023[88]
Decitabine	1	50	Powder	970.86	19.42	MIMS 2023[88]
Interferon alfa	1	3	Pre-filled syringe	14.20	4.73	MIMS 2023[88]
Peginterferon alfa-2a	1	90	Pre-filled syringe	76.51	0.85	MIMS 2023[88]
Peginterferon alfa-2a	1	135	Pre-filled syringe	107.76	0.80	MIMS 2023[88]
Peginterferon alfa-2a	4	180	Pre-filled syringe	497.6	0.69	MIMS 2023[88]

BNF = British National Formulary; eMIT = electronic market information tool; MIMS = Monthly Index of Medical Specialties.

Note: Due to the distribution of treatment used in the model and based on the FREEDOM-2 data, only interferon-alpha incurs intravenous costs. The other drugs are not used in the BAT treatment basket in the base case.

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The DES model enables acquisition costs to be accumulated at the point of prescription and administration. This ensures that wastage due to death or discontinuation is included.

B.3.5.1.2 Ruxolitinib costs

Ruxolitinib is a potent and selective JAK-1/JAK-2 inhibitor that has demonstrated superiority over placebo and BAT[69] and that allows patients to achieve significant response in spleen reduction at week 24, as well as significant reduction in symptoms associated with myelofibrosis.

Ruxolitinib is often given depending on the patient platelet count, with patients having a lower platelet count receiving a lower dose of ruxolitinib. Ruxolitinib is available in the following doses:

- 5 mg twice daily (recommended for platelet counts 50,000-100,000 per µL)
- 10 mg twice daily
- 15 mg twice daily (recommended for platelet counts 100,000-200,000 per µL)
- 20 mg twice daily (recommended for platelet counts > 200,000 per µL)

Ruxolitinib is given orally twice daily, with a maximum dose of 25 mg twice daily.[92]

In the original fedratinib submission to NICE, ruxolitinib costing was based on the distribution of platelet counts, using the dosing schedule outlined above. FREEDOM-2 provided the distribution of patients receiving different doses of ruxolitinib, and additional analyses have been undertaken to present a more granular dosing of ruxolitinib, as presented in Table 61 for the first 6 treatment cycles. This removed the need to have a differentiation by platelet count in the economic model. Therefore, the functionality to include only patients below or above the 100,000 platelet count per litre has been removed from the model, and the observed distribution of ruxolitinib by daily dose is used instead. Of note, patients can receive more than one dose of ruxolitinib per cycle; hence, proportions can exceed 100%. The FREEDOM-2 trial also presented the mean dose (24.1 mg) for ruxolitinib. The impact of using this dose was explored in the scenario analysis.

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Table 61. Ruxolitinib dose distribution

All daily dose	No. of patients (%)						Source
	EOC1	EOC2	EOC3	EOC4	EOC5	EOC6	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Additional analysis FREEDOM-2[36]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Additional analysis FREEDOM-2[36]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Additional analysis FREEDOM-2[36]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Additional analysis FREEDOM-2[36]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Additional analysis FREEDOM-2[36]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Additional analysis FREEDOM-2[36]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Additional analysis FREEDOM-2[36]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Additional analysis FREEDOM-2[36]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Additional analysis FREEDOM-2[36]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Additional analysis FREEDOM-2[36]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Additional analysis FREEDOM-2[36]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Additional analysis FREEDOM-2[36]

EOC = end of cycle.

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Considering the dosing range of ruxolitinib is 5 mg through 20 mg, as per the SmPC, doses beyond 25 mg are considered as an alteration of dosing and are considered as an increase in dosing, making the use of RDI inappropriate for ruxolitinib because the RDI would be double counting the dose modification.

Ruxolitinib is available in 4 different strengths: 5 mg, 10 mg, 15 mg, and 20 mg. The costs are presented in Table 62. In the model, the percentage of patients receiving each dose (5-40 mg) twice daily is calculated. For example, patients receiving 15 mg will receive 1 dose of 5 mg and 1 dose of 10 mg once daily. The distribution of ruxolitinib doses provided in Table 62 is based on the initial dose and the doses (in mg) received at the end of each cycle until cycle 6. To estimate the proportion of patients receiving each dose strength (i.e., 5 mg, 10 mg, 15 mg and so on), the total number of patients receiving the dose strength was summed across the 6 cycles and was then divided by the total number of patients who received an initial dose. In practice, this is received twice daily. Hence, an assumption is required about how the daily dose is split. With the exception of the 15 mg strength dose, all daily doses were even and therefore assumed to be received as 2 equal doses. For the 15 (and 25) mg daily dose, it was assumed that this represented a 5 mg tablet and a 10 (or 20) mg tablet. For the 35 mg daily dose, it was assumed that this represented a 15 mg tablet and a 20 mg tablet For a 50 mg daily dose, it is assumed that this represents use of 20 mg and 5 mg twice daily, whilst a daily dose of 80 mg represents use of two 20 mg tablets twice daily.

Table 62. Ruxolitinib cost

Ruxolitinib cost	Price (£)	Source
5 mg tablet, 56 in pack	1,428.00	Jakavi, MIMS 2023[91]
10 mg tablet, 56 in pack	2,856.00	Jakavi, MIMS 2023[91]
15 mg oval tablet, 56 in pack	2,856.00	Jakavi, MIMS 2023[91]
20 mg elongated tablet, 56 in pack	2,856.00	Jakavi, MIMS 2023[91]

MIMS = Monthly Index of Medical Specialties.

Table 63. Ruxolitinib data used in the cost-effectiveness model

Strength of ruxolitinib	Distribution used in the model
5 mg	[redacted]
10 mg	[redacted]
15 mg	[redacted]
20 mg	[redacted]
25 mg	[redacted]
30 mg	[redacted]
35 mg	[redacted]
40 mg	[redacted]
50 mg	[redacted]
80 mg	[redacted]

B.3.5.1.3 Administration costs

Oral treatments (such as JAK inhibitors) are assumed to have no associated administration costs. Treatments administered by injection are assigned a flat cost per administration taken from NHS Reference Costs (Table 64).

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Table 64. Unit costs of administration

Method of administration	Cost (£)	Description	Source
Injection	368	Per administration	NHS Reference Costs 2021-22, SB15Z (deliver subsequent elements of a chemotherapy cycle)[93]
Oral	0	Per prescription[a]	Assumption
Self-administration	0	Per administration	Assumption

[a] The model contains the option for oral administration costs to be applied per prescription or as a flat rate per 4-week model cycle.

B.3.5.1.4 Subsequent treatments

Due to the progressive nature of the disease, patients are likely to receive more than 1 treatment.

In the model, only BAT is included as a subsequent therapy to be given after fedratinib when patient discontinues fedratinib. The composition of BAT after fedratinib slightly differs from the composition of BAT as a comparator because treatments received by the patients depend on whether there is a response or no response. If the patient responds and goes on to receive BAT, then fedratinib will be included in the BAT basket and will be labelled as suboptimal fedratinib. If the patient does not respond and go on to receive BAT, fedratinib will not be included in the BAT basket and the remaining treatments will be reweighted. Table 65 summarises the proportion of patients receiving each treatment in subsequent BAT. Patients receiving BAT as initial therapy are not subject to receive a subsequent therapy.

Table 65. Subsequent BAT composition

Treatment	BAT (after fedratinib, responders)	BAT (after fedratinib, non-responders)
Danazol	5.8%	16.7%
Hydroxycarbamide (hydroxyurea)	5.8%	16.7%
Interferon alfa	5.8%	16.7%
Prednisolone	5.8%	16.7%
Prednisone	5.8%	16.7%
Thalidomide	5.8%	16.7%
Ruxolitinib	0%	0%
Fedratinib	65%	0%

BAT = best available therapy.

The costs associated with subsequent treatments are the same as those presented in Table 60.

B.3.5.2 Health-state unit costs and resource use

The following subsections detail the health-state costs and resource use.

B.3.5.2.1 Monitoring and other resource utilisation

The FREEDOM-2 clinical trial did not provide resource use estimates. Instead, the resource use in the model was primarily informed by the ruxolitinib NICE submission, which leveraged data from 3 sources:

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- Haematological Malignancy Research Network (HMRN) audit (2016)[94]: UK audit of clinical management, resource utilisation and outcome in primary and secondary myelofibrosis.
- The ROBUST study[95]: a phase 2 study that was done in the UK (n = 48). It included patients with intermediate-1, intermediate-2, and high-risk disease.
- The JUMP study[96]: A phase 3 expanded-access trial designed to assess the safety and efficacy of ruxolitinib in patients with high-risk, intermediate-2 risk, or intermediate-1 risk disease. This study did not include any patients from the UK.

The HMRN audit in 2016 and the ROBUST study were UK-specific studies[94,95] and were used to inform resource use for patients receiving BAT. The ruxolitinib NICE submission used either assumptions or the JUMP study[96] to inform the change in resource use associated with ruxolitinib, relative to BAT. The HMRN audit in 2016 assessed a time period when ruxolitinib was approved in the CDF by NICE. Where possible, inputs were updated using the HMRN 2020 audit. The updated HMRN audit also included resource use for patients who received ruxolitinib, so this was used to recalculate the relative impact of a JAK inhibitor on resource use over time. The base-case assumptions for the model apply the values used in TA386 and TA756.

Table 66 presents the resource used per week for BAT and supportive care.

Table 66. Resource use per week for the BAT arm and supportive care

Resource	Use per week	Source
BAT resource use		
A&E visit	0.013	ROBUST - NICE (2016), TA386, Committee papers (ACD), Table 47[95]
FBC and U&E	0.320	HMRN audit - NICE (2016), TA386, Committee papers (ACD), Table 47[94]
Hospital night	0.150	HMRN audit - NICE (2016), TA386, Committee papers (ACD), Table 47[94]
Outpatient visit	0.220	HMRN audit - NICE (2016), TA386, Committee papers (ACD), Table 47[94]
Primary care visit	0.030	ROBUST - NICE (2016), TA386, Committee papers (ACD), Table 47[95]
RBC unit transfusion	0.160	Assumption - NICE (2016), TA386, Committee papers (ACD), Table 47[10]
Urgent care	0.003	ROBUST - NICE (2016), TA386, Committee papers (ACD), Table 47[95]
Supportive care		
A&E visit	0.013	Assumed equal to BAT, TA386[10]
FBC and U&E	0.160	50% lower than BAT, TA386[10]
Hospital night	0.150	Assumed equal to BAT, TA386[10]
Outpatient visit	0.110	50% lower than BAT, TA386[10]
Primary care visit	0.030	Assumed equal to BAT, TA386[10]
RBC unit transfusion	0.160	COMFORT-I placebo arm, TA386[10]
Urgent care	0.003	Assumed equal to BAT, TA386[10]

A&E = accident and emergency; ACD = Appraisal Consultation Document; BAT = best available therapy; FBC = full blood count; RBC = red blood cell; U&E = urea and electrolytes.

For fedratinib, percentage differences in resource utilisation relative to BAT are entered for each of these periods as reported in NICE TA386 and TA756 (Table 67).

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Table 67. Resource use for fedratinib based on NICE TA386 and used in TA756

Resource	Up to week 12	Up to week 24	Up to week 36	Up to week 48	Up to week 108	Up to week 144	Beyond week 144	Source
A&E visit	0.00%	−51.70%	−73.30%	−72.00%	−96.40%	−96.40%	−96.40%	JUMP: NICE (2016), TA386, Committee papers (ACD), Table 47
FBC and U&E	+4.00%	−83.60%	−82.60%	−82.60%	−82.60%	−82.60%	−82.60%	Assumptions: NICE (2016), TA386, Committee papers (ACD), Table 47
Hospital night	0.00%	−66.30%	−80.60%	−85.80%	−100.00%	−100.00%	−100.00%	JUMP: NICE (2016), TA386, Committee papers (ACD), Table 47
Outpatient visit	+51.51%	−74.74%	−74.74%	−74.74%	−74.74%	−74.74%	−74.74%	Assumptions: NICE (2016), TA386, Committee papers (ACD), Table 47
Primary care visit	0.00%	−36.70%	−58.20%	−81.70%	−97.70%	−97.70%	−97.70%	JUMP: NICE (2016), TA386, Committee papers (ACD), Table 47
RBC unit transfusion	+43.30%	+43.30%	+10.00%	+10.00%	+10.00%	−23.30%	−58.30%	Assumptions: NICE (2016), TA386, Committee papers (ACD), Table 47
Urgent care	0.00%	−51.50%	−100.00%	−93.10%	−93.10%	−93.10%	−93.10%	JUMP: NICE (2016), TA386, Committee papers (ACD), Table 47

A&E = accident and emergency; ACD = Appraisal Consultation Document; FBC = full blood count; RBC = red blood cell; U&E = urea and electrolytes.

Sources: NICE[10]; NICE[65]

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Thiamine costs are included in the model because, for patients receiving fedratinib, low thiamine levels should be supplemented. Thiamine testing is conducted alongside routine tests; therefore, no extra visits are required. The frequency of thiamine testing is once every month for the first 3 months, then once every 3 months. These visits are captured by the frequency of full blood counts and U&E testing, already being applied in the model. Table 68 presents the cost of a thiamine test, percentage of patients requiring thiamine, and average milligrams needed per day.

Table 68. Thiamine parameters used in the model

Parameter	Value	Source
Cost of thiamine test	£44	NHS Reference cost - 2021-22 (DAPS02)[93]
Percentage of patients requiring thiamine	23.13%	FREEDOM-2 CSR, Table 8.7.3-1[36]
Thiamine average mg required daily	200 mg	Assumption (50-300 mg taken per day according to severity)

CSR = case report form; NHS = National Health Service.

The unit cost of each resource is presented in Table 69. Costs have been taken from the latest NHS reference cost and Personal Social Services Research Unit (PSSRU) document and have been inflated to 2022 where relevant by using inflation indices from the PSSRU 2022.

Table 69. Resource use unit costs

Resource	Unit cost	Source
A&E visit	143.74	NHS Reference Costs 2021-22 (A&E)[93]
FBC and U&E	74.27	Private Patient Tariff 2019 (Dorset County Hospital, full blood count and U&E profile), inflated to 2022[97]
Hospital night	756.23	NHS Reference Costs 2021-22 (non-elective inpatients excess bed day)[93]
Outpatient visit	209.41	NHS Reference Costs 2021-22 (WF01A - clinical haematology, non-admitted face-to-face)[93]
Primary care visit	41.00	PSSRU unit costs 2022 (general practitioner consultation)[98]
RBC unit transfusion	391.63	Varney and Guest (2003)[99] (cost per RBC unit), inflated to 2022
Urgent care	150.33	PSSRU unit costs 2022 (acute medical unit)[98]

A&E = accident and emergency; FBC = full blood count; NHS = National Health Service; PSSRU = Personal Social Services Research Unit; RBC = red blood cell; U&E = urea and electrolytes.

Table 70 summarises costs incurred by each treatment.

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Table 70. Summary of resource costs used in the cost-effectiveness model

Cost per week	Fedratinib	BAT as comparator	BAT after fedratinib (responders)	BAT after fedratinib (non-responders)	Supportive care
Cost per week (£), 0-12 weeks	301.30	289.70	249.48	249.48	226.31
Cost per week (£), 12-24 weeks	145.96	168.93	249.48	249.48	226.31
Cost per week (£), 24-36 weeks	107.72	139.46	249.48	249.48	226.31
Cost per week (£), 36-48 weeks	101.65	134.74	249.48	249.48	226.31
Cost per week (£), 48-108 weeks	84.83	121.69	249.48	249.48	226.31
Cost per week (£), 108-144 weeks	63.96	105.50	249.48	249.48	226.31
Cost per week (£), 144+ weeks	42.03	88.47	249.48	249.48	226.31

BAT = best available therapy.

B.3.5.3 Adverse reaction unit costs and resource use

Adverse event costs were largely taken from the NHS Reference Costs, the PSSRU Unit Cost of Health and Social Care,[98] and other sources identified in both the ruxolitinib and fedratinib NICE submissions. Where NHS Reference Costs were used, weighted averages of relevant currency/service codes were calculated. Sources were consistent with those selected for the ruxolitinib and fedratinib NICE submissions, with values taken from updated publications where available. The cost of AML was taken from a study by Wang et al.[100] that considered medical costs of AML calculated using a microcosting approach. The microcosting analysis included costs associated with treatment, hospitalisations, diagnostic tests, transfusions, and associated complications.

Table 71 presents unit costs for AEs. Table 72 presents AE costs per year. Where the costs are not from 2022, they are inflated to 2022 using the PSSRU inflation indices.[98]

Table 71. Grade 3+ adverse event costs included in the cost-effectiveness model

Adverse event	Cost (2022 £)	Source
Abdominal pain	756.07	NHS Reference Costs 2021-22 (weighted average: FD05A - abdominal pain with interventions, FD05B - abdominal pain without interventions)[93]
Acute kidney injury	2,113.27	NHS Reference Costs 2021-22 (weighted average: LA07L-P - acute kidney injury without Interventions, with CC score 0-12+)[93]
ALT increase	2,057.98	NHS Reference Costs 2021-22 (weighted average: GC17A-K non-malignant, hepatobiliary or pancreatic disorders, without Interventions, with CC score 0-9+)[93]

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Adverse event	Cost (2022 £)	Source
AST increase	2,057.98	NHS Reference Costs 2021-22 (weighted average: GC17A-K non-malignant, hepatobiliary or pancreatic disorders, without interventions, with CC score 0-9+)[93]
Asthenia	13.53	NICE 2014, TA316, evaluation report 4, Table 68[101]
Atrial fibrillation	41.90	PSSRU 2022 (general practitioner consultation) & MIMS 2023 (course of loperamide)[98]
Cardiac congestive failure	2,382.38	NHS Reference Costs 2021-22 (weighted average: EB05A-C - cardiac arrest with CC score 0-9+)[93]
Chronic kidney injury	2,200.51	NHS Reference Costs 2021-22 (weighted average: LA08K-P - chronic kidney disease without interventions, with CC score 0-11+)[93]
Decreased appetite	801.11	NHS Reference Costs 2021-22 (non-elective inpatient short-stay)[93]
Diarrhoea	41.90	PSSRU 2022 (general practitioner consultation) & MIMS 2023 (course of loperamide)[98]
Dyspnoea	862.68	NHS Reference Costs 2021-22 (weighted average: DZ19H-J other respiratory disorders with multiple interventions)[93]
Emphysema	862.68	NHS Reference Costs 2021-22 (weighted average: DZ19H-J other respiratory disorders with multiple interventions)[93]
Gastrointestinal haemorrhage	1,568.31	NHS Reference Costs 2021-22 (weighted average: FD03C-FD03H: gastrointestinal bleed without interventions, with CC score 0-8+)[93]
General physical health deterioration	1,186.77	NHS Reference Costs 2021-22 (weighted average: HC32G-HC32K low back pain with and without interventions)[93]
Glomerular filtration rate decreased	753.88	NHS Reference Costs 2021-22 (single cost: WJ11Z other disorders of immunity)[93]
Hyperkalaemia	1,674.08	NHS Reference Costs 2021/22 (weighted average: KC05G-N fluid or electrolyte disorders, without/with Interventions, with CC score 0-10+)[93]
Hypokalaemia	1,674.08	NHS Reference Costs 2021/22 (weighted average: KC05G-N fluid or electrolyte disorders, without/with interventions, with CC score 0-10+)[93]
Hyponatraemia	1,674.08	NHS Reference Costs 2021/22 (weighted average: KC05G-N fluid or electrolyte disorders, without/with interventions, with CC score 0-10+)[93]
Pneumonia	1,531.34	NHS Reference Costs 2021/22 (weighted average: DZ22M-Q unspecified acute lower respiratory infection without interventions, with CC score 0-13+)[93]
Renal failure	1,757.91	NHS Reference Costs 2021/22 (weighted average: LA09J-Q general renal disorders without/with interventions, with CC score 0-6+)[93]
Renal impairment	1,757.91	NHS Reference Costs 2021/22 (weighted average: LA09J-Q general renal disorders without/with interventions, with CC score 0-6+)[93]
Transformation to AML	58,865.21	Wang et al. (2014)[100]

ALT = alanine aminotransferase; AML = acute myeloid leukaemia; AST = aspartate aminotransferase; CC = comorbidity and complications; MIMS = Monthly Index of Medical Specialities; NHS = National Health Service; PSSRU = Personal Social Services Research Unit.

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Table 72. Annual costs of adverse events in the model

Treatment	Annual cost of AEs (£)
Fedratinib	877
BAT (as comparator)	283
BAT (after fedratinib)	283

AE = adverse event; BAT = best available therapy.

B.3.5.4 Miscellaneous unit costs and resource use

The model does not include any other unit costs and resource use besides the ones that were shown in previous sections.

B.3.5.4.1 End-of-life costs

In the model, end-of-life costs are applied as a one-off cost upon death. The cost for the end-of-life care health state was identified from a study by Round et al.[102] that estimated the health and social costs of patients with cancer in the final weeks of life. This source is consistently used in NICE myelofibrosis appraisals, making it reasonable to be used in the cost-effectiveness model despite being several years old. These costs were inflated to the current model cost year. A study by Addicott and Dewar[103] that estimated the cost of care in the final 8 weeks of life is presented as an additional option in the model. The source used is consistent with that used for the end-of-life cost applied in the ruxolitinib NICE submission. Table 73 presents the available options for costing the supportive care health state.

Table 73. End-of-life costs

Health state	One-off cost per patient (£)	Source	Original price year
Supportive care	6,439	Addicott and Dewar[104]	2008
	6,510	Round et al.[102]	2014

Note: Costs were inflated to a consistent price year in the model. Underlined values represent the values used in the base case of the model.

B.3.6 Severity

The conditions for applying severity weight are not met for this technology.

B.3.7 Summary of base-case analysis inputs and assumptions

B.3.7.1 Summary of base-case analysis inputs

Appendix J summarises the base-case analysis inputs and the sources of data used for each parameter.

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B.3.7.2 Assumptions

Table 74. Assumptions in the economic model

Category	Assumption	Justification	Reference in submission
Response	"Spleen or symptom response" is the most appropriate definition for response.	IWG-MRT guidelines suggest both types of response should be considered. This was also substantiated by clinical experts.	B.3.3: types of responses
	Response is defined as ≥ 35% SVR.	This level of SVR is considered by the IWG-MRT and ELN as appropriate for response in patients with myelofibrosis.	B.3.3.4: Spleen volume reduction or total symptom score response rates
OS	OS is assumed to be equal to BAT.	This is due to limitations in crossover analysis.	B.2.6.1.6: FREEDOM-2: overall survival crossover adjustment
	OS for fedratinib is based on a Weibull curve extrapolation.	The Weibull curve was selected because it closely matches the data and is aligned with clinician's expectations	B.3.3.6.2: Overall survival
Discontinuation	TTD for fedratinib is set equal to BAT.	This is due to limitations in crossover analysis.	B.3.3.6.1: Overview of survival analyses conducted for the economic model
BAT	The base-case OS for BAT is based on a Weibull curve.	The Weibull curve was selected because it closely matches the data and aligns with clinician expectations.	B.3.3.6.2: Overall survival
Utilities	Utility is dependent on patient response as opposed to treatment arm.	Baseline utility and the utility values that depend on response status are informed by analyses of FREEDOM-2 data.	B.3.4.2: Mapping
Suboptimal fedratinib	Fedratinib given in subsequent BAT treatment for those who responded to treatment.	All patients who had not discontinued fedratinib (32.1%) would continue fedratinib as part of BAT.	B.3.2.3: Intervention technology and comparators
AEs	Only non-haematological AEs grade ≥ 3 are explicitly modelled.	The impacts of thrombocytopenia, anaemia, and neutropenia (common AEs in myelofibrosis) on costs and utilities are assumed to be captured elsewhere by the model.	B.3.3.5: Adverse events

AE = adverse event; BAT = best available therapy; ELN = European LeukemiaNet; IWG-MRT = International Working Group-Myeloproliferative Neoplasms Research and Treatment; OS = overall survival; SVR = spleen volume reduction; TTD = time to deterioration.

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B.3.8 Base-case results

Base-case incremental cost-effectiveness analysis results

This section reports the discounted base-case deterministic results for the population of interest. All results are presented with the confidential patient access scheme (PAS) for fedratinib applied. In this setting, 10,000 patients have been used in the simulation. Table 75 presents the discounted total costs, as well as LYs and QALYs of fedratinib and BAT. When compared with BAT and using pooled fedratinib/BAT for OS and TTD (i.e., no benefit from one treatment over the other for survival outcomes) in the base case, the ICER for fedratinib is dominant (i.e., less costly and giving more QALYs than the comparator of BAT). The incremental costs are [redacted] lower for fedratinib. Therefore, fedratinib, using a conservative approach, dominates BAT and would be considered cost-effective because it results in improved health outcomes while reducing costs to the NHS.

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Table 75. Base-case results

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER incremental (£ per QALY)
BAT	[redacted]	[redacted]	[redacted]				
Fedratinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant [redacted]

BAT = best available therapy; ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality-adjusted life-year.

Table 76. Net health benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000 (£)	NHB at £30,000 (£)
BAT	[redacted]	[redacted]				
Fedratinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BAT = best available therapy; NHB = net health benefit; QALY = quality-adjusted life-year.

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Table 77 shows costs disaggregated by health state for fedratinib and BAT. The largest difference in costs is accrued in the BAT health state. Overall, the incremental cost over the lifetime is [redacted] per patient.

Table 77. Pairwise cost comparison by health state

	Cost (£)		
Health state	**BAT**	**Fedratinib**	**Incremental**
JAKi state	[redacted]	[redacted]	[redacted]
BAT state	[redacted]	[redacted]	[redacted]
Supportive care state	[redacted]	[redacted]	[redacted]
Death (end of life)	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

BAT = best available therapy; JAKi = Janus kinase inhibitor.

Table 78 shows the costs disaggregated by resource category for fedratinib and BAT. As expected, drug acquisition costs are the primary cost in both arms. Cost savings are observed in drug administration for fedratinib relative to BAT because fedratinib is administered orally, and administration costs are only accrued once the patient transitions to BAT. Other resource categories show marginal differences, with higher costs for fedratinib for all but resource use in the supportive care state and end-of-life costs (discounted).

Table 78. Pairwise cost comparison by health state and resource category

	Cost (£)		
Health state	**BAT**	**Fedratinib**	**Incremental**
Acquisition	[redacted]	[redacted]	[redacted]
JAKi state	[redacted]	[redacted]	[redacted]
BAT state	[redacted]	[redacted]	[redacted]
Supportive care state	[redacted]	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]
JAKi state	[redacted]	[redacted]	[redacted]
BAT state	[redacted]	[redacted]	[redacted]
Supportive care state	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]
JAKi state	[redacted]	[redacted]	[redacted]
BAT state	[redacted]	[redacted]	[redacted]
Supportive care state	[redacted]	[redacted]	[redacted]
Resource use	[redacted]	[redacted]	[redacted]
JAKi state	[redacted]	[redacted]	[redacted]
BAT state	[redacted]	[redacted]	[redacted]
Supportive care state	[redacted]	[redacted]	[redacted]
Thiamine testing and supplementation	[redacted]	[redacted]	[redacted]
End of life	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

BAT = best available therapy; JAKi = Janus kinase inhibitor.

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Table 79 and Table 80 present a breakdown of LYs and QALYs gained. The results suggest that fedratinib improves QOL (0.167 incremental QALYs) relative to BAT for patients with myelofibrosis. This is due to the better response with fedratinib, which is associated with improved utility. Of note, there is no gain in LYs between the 2 treatments because the pooled fedratinib/BAT survival function is in use in the model base case.

Table 79. Pairwise comparison of life-years

	LYs		
Health state	**BAT**	**Fedratinib**	**Incremental**
JAKi state	0.000	2.046	2.046
BAT state	2.046	0.457	−1.589
Supportive care	1.385	0.928	−0.457
Total	3.431	3.431	0.000

BAT = best available therapy; JAKi = Janus kinase inhibitor; LY = life-year.

Table 80. Pairwise comparison of QALYs

	QALYs		
Health state	**BAT**	**Fedratinib**	**Incremental**
JAKi state	0.000	1.389	1.389
BAT state	1.254	0.267	−0.987
Supportive care	0.725	0.491	−0.234
Total	1.979	2.147	0.167

BAT = best available therapy; JAKi = Janus kinase inhibitor; QALY = quality-adjusted life-year.

B.3.9 Exploring uncertainty

To explore the uncertainty of parameter precision, choice of data sources, and modelling assumptions, probabilistic and deterministic sensitivity analyses as well as scenario analyses were conducted.

Probabilistic sensitivity analysis

The probabilistic sensitivity analysis results are based on 500 repeated simulations that drew from the distributions of parametric functions, costs, and utility values. The number of replications was considered sufficient because the expected values of incremental QALYs and costs by the number of replications demonstrated stability well before 500 replications. Table 81 presents probabilistic sensitivity analysis output for the discounted total costs, LYs, and QALYs of fedratinib and BAT; these results are consistent with the deterministic results.

Figure 42 presents the incremental cost-effectiveness plane. For all iterations, results are in the southeast quadrant, as use of fedratinib results in a QALY gain and cost saving. Hence, for all probabilistic iterations, fedratinib dominates BAT. Figure 43 presents the cost-effectiveness acceptability curve, in which fedratinib has a 100% probability of being cost-effective at any WTP threshold between £0 and £100,000.

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Table 81. Incremental and pairwise probabilistic sensitivity analysis results

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER vs. baseline (£ per QALY)
BAT	[redacted]	[redacted]	[redacted]				
Fedratinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant [redacted]

BAT = best available therapy; ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality-adjusted life-year.

Figure 42. Incremental cost-effectiveness plane

ICER = incremental cost-effectiveness ratio; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year; WTP = willingness to pay.

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Figure 43. Cost-effectiveness acceptability curve

ICER = incremental cost-effectiveness ratio; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year; WTP = willingness to pay.

Deterministic sensitivity analysis

Deterministic sensitivity analysis was conducted comparing fedratinib with BAT. The analysis varied the key model settings, efficacy inputs, costs, and utility values across the variance, if the variance in any input was not available, an assumption was made that the standard error was 10% of the mean value. Results are presented in Table 82 and as a tornado diagram in Figure 44. Given that fedratinib dominated BAT, the tornado diagram for the deterministic sensitivity analyses is constructed based on incremental net monetary benefits based on a WTP threshold of £30,000 to facilitate interpretation of the results. Fedratinib remains the dominant treatment option in all the scenarios tested, with the largest change observed when parameters relating to AEs are changed. However, those variations have a minimal impact on the ICER.

Table 82. One-way sensitivity analysis results

	£/QALY		
Parameter name	**ICER at lower bound**	**ICER at upper bound**	**Difference**
Disutility per event: general physical health deterioration (0.18-0.26)	[redacted]	[redacted]	[redacted]
FREEDOM-2: annual AEs: general physical health deterioration - fedratinib (0.06-0.09)	[redacted]	[redacted]	[redacted]
Beyond week 144 - RBC unit transfusion (−0.47 to −0.69)	[redacted]	[redacted]	[redacted]

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Parameter name	£/QALY		
	ICER at lower bound	ICER at upper bound	Difference
Cost per event: hyperkalaemia (1,345.97-2,002.19)	[redacted]	[redacted]	[redacted]
FREEDOM-2: annual AEs: acute kidney injury - fedratinib (0.05-0.08)	[redacted]	[redacted]	[redacted]
Beyond week 144 - outpatient visit (−0.59 to −0.88)	[redacted]	[redacted]	[redacted]
FREEDOM-2: annual AEs: hyperkalaemia - fedratinib (0.06-0.10)	[redacted]	[redacted]	[redacted]
Disutility per event: ALT increased (0.12-0.18)	[redacted]	[redacted]	[redacted]
Cost per event: acute kidney injury (1,699.07-2,527.46)	[redacted]	[redacted]	[redacted]
Up to week 108 - outpatient visit (−0.59 to −0.88)	[redacted]	[redacted]	[redacted]

AE = adverse event; ALT = alanine aminotransferase; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; RBC = red blood cell.

Figure 44. One-way sensitivity analysis tornado plot presenting the most influential parameters

AE = adverse event; ALT = alanine aminotransferase; BAT = best available therapy; ICER = incremental cost-effectiveness ratio; RBC = red blood count.

Scenario analysis

Scenario analyses were undertaken to investigate the effect of certain model inputs on costs and outcomes. Table 83 presents the scenarios conducted and the rational for each scenario as well as the ICER. Of note, the scenarios presented have been run with the response endpoint being “SVR or TSS.” It can be noted that, in most scenarios presented below, fedratinib is cost-effective.

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Table 83. Scenario analysis overview and results

Scenario	Scenario detail	Brief rationale	ICER (£/QALY)
Base case			[redacted] (fedratinib dominates)
OS equal in fedratinib and BAT; TTD equal in fedratinib and BAT. Distributions assigned: ▪ FED OS: Gompertz ▪ FED TTD: log-logistic ▪ BAT OS: Gompertz ▪ BAT TTD: log-logistic	Equal OS for fedratinib and BAT and equal TTD for fedratinib and BAT; OS curves follow the Weibull parametrisation.	Tests the impact of changing the distribution assumption for OS. The Gompertz distribution is identified by the AIC and BIC as the second−best distribution when also considering clinically plausible survival at 20 years.	[redacted] (fedratinib dominates)
OS equal in fedratinib and BAT; TTD equal in fedratinib and BAT. Distributions assigned: ▪ FED OS: Weibull ▪ FED TTD: gen gamma ▪ BAT OS: Weibull ▪ BAT TTD: gen gamma	Equal OS for fedratinib and BAT and equal TTD for fedratinib and BAT. TTD curves follow the gen-gamma parametrisation.	Tests the impact of changing the distribution assumption for TTD. The gen-gamma distribution is identified by the AIC and BIC as the second-best distribution.	[redacted] (fedratinib dominates)
OS and TTD separated only by treatment. Distributions assigned: ▪ FED OS: Weibull ▪ FED TTD: exponential ▪ BAT OS: Weibull ▪ BAT TTD: exponential	OS and TTD analyses are presented by treatment (i.e., fedratinib and BAT), although there is no differentiation with response status.	Captures the impact of treatment difference in response on outcomes.	[redacted] (fedratinib dominates)
OS equal in fedratinib and BAT; separate TTD. ▪ FED OS: Weibull ▪ FED TTD: exponential ▪ BAT OS: Weibull ▪ BAT TTD: exponential	Equal OS for fedratinib and BAT with separate TTD.	Assumes the same survival for fedratinib and BAT but allows for different TTD.	[redacted] (fedratinib dominates)
Equal OS and TTD for fedratinib and BAT. ▪ FED OS: Weibull ▪ FED TTD: log-logistic ▪ BAT OS: Weibull ▪ BAT TTs: log-logistic Does not include AE disutility. Does not include worsening utility on supportive care to both fedratinib and BAT.	Assumes no adverse event disutility and worsening utility on supportive care.	Tests the impact of assuming no adverse utility disutility and worsening utility on supportive care.	[redacted] (fedratinib dominates)
No crossover for BAT ▪ FED OS: Weibull ▪ BAT OS: log-logistic ▪ FED TTD: log-logistic	Patients do not crossover for BAT.	Tests the impact of the assumption of no crossover for BAT.	[redacted]

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Scenario	Scenario detail	Brief rationale	ICER (£/QALY)
▪ BAT TTD: log-logistic			
OS and TTD separated only by treatment. Distributions assigned: ▪ FED OS: log-normal ▪ FED TTD: log-normal ▪ BAT OS: Weibull ▪ BAT TTD: log-logistic	OS and TTD analyses are presented by treatment (i.e., fedratinib and BAT), although there is no differentiation with response status. Alternative distributions are used.	Captures the impact of treatment difference in response on outcomes. Understands how alternative distributions impact the results.	[redacted]
OS and TTD are split by treatment and response status. Distributions assigned: ▪ FED OS NR: log-normal ▪ FED OS R: log-normal ▪ FED TTD NR: log-logistic ▪ FED TTD R: gen gamma ▪ BAT OS NR: Weibull ▪ BAT OS R: no crossover: log-normal ▪ BAT TTD NR: exponential ▪ BAT TTD R: gen gamma	OS and TTD analyses are presented by treatment and are split by response status (i.e., responder or non-responder).	Assesses the relationship of response on OS and response's influence on TTD and checks impact on results.	[redacted]
OS and TTD are split by treatment and response status. Distributions assigned: ▪ FED OS NR: Weibull ▪ FED OS R: Weibull ▪ FED TTD NR: log-normal ▪ FED TTD R: log-normal ▪ BAT OS NR: log-normal ▪ BAT OS R: no crossover: log-normal ▪ BAT TTD NR: exponential ▪ BAT TTD R: gen gamma	OS and TTD analyses are presented by treatment and are split by response status (i.e., responder or non-responder). Alternative distributions are used.	Assesses the relationship of response on OS and response's influence on TTD and checks impact on results. Understands how alternative distributions impact the results.	[redacted] (fedratinib dominates)
Responder scenario 1: OS is split by treatment and response status. TTD remains pooled FED/BAT. Distributions assigned: ▪ FED OS NR: Weibull ▪ FED OS R: Weibull ▪ BAT OS NR: log-logistic ▪ BAT OS R (pooled FED/BAT): Weibull Suboptimal FED: 0%	OS is split by treatment and response status. TTD remains pooled between fedratinib and BAT.	Assesses OS benefit based on response.	[redacted] (fedratinib dominates)
Responder scenario 2: OS is split by treatment and	OS is split by treatment and response status. TTD remains pooled	Assesses OS benefit based on response	[redacted] (fedratinib dominates)

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Scenario	Scenario detail	Brief rationale	ICER (£/QALY)
response status. TTD remains pooled FED/BAT. Distributions assigned: ▪ FED OS NR: exponential ▪ FED OS R: exponential ▪ BAT OS NR: log-normal ▪ BAT OS R (pooled FED/BAT): exponential Suboptimal fed: 0%	between fedratinib and BAT. Alternative distributions are assigned (2nd best).		
Responder scenario 1: OS is split by treatment and response status. TTD remains pooled FED/BAT. Distributions assigned: ▪ FED OS NR: Weibull ▪ FED OS R: Weibull ▪ BAT OS NR: log-logistic ▪ BAT OS R (pooled FED/BAT): Weibull Suboptimal fed: 32.1%	Same as above, but suboptimal fedratinib has been increased to 32.1%.	Checks the impact of more patients receiving suboptimal fedratinib.	[redacted] (fedratinib dominates)
Responder scenario 2: OS is split by treatment and response status. TTD remains pooled FED/BAT. Distributions assigned: ▪ FED OS NR: exponential ▪ FED OS R: exponential ▪ BAT OS NR: log-normal ▪ BAT OS R (pooled FED/BAT): exponential Suboptimal fed: 32.1%	Same as above	As above	[redacted] (fedratinib dominates)
Fedratinib in BAT after fedratinib treatment: 25%	As above	As above	[redacted] (fedratinib dominates)
Fedratinib in BAT after fedratinib treatment: 50%	As above	As above	[redacted] (fedratinib dominates)
Fedratinib in BAT after fedratinib treatment: 65%	As above	As above	[redacted] (fedratinib dominates)
Use of mean dose for ruxolitinib dosing in BAT	The mean initial dose based on the FREEDOM-2 CSR is used in the model.	Assess the impact of a fixed dose. In this scenario, wastage is included.	[redacted] (fedratinib dominates)

AE = adverse event; AIC = Akaike information criterion; BAT = best available therapy; BIC = Bayesian information criterion; FED = fedratinib; ICER = incremental cost-effectiveness ratio; NR = non-response; OS = overall survival; QALY = quality-adjusted life-year; R = response; TTD = time to treatment discontinuation.

B.3.10 Subgroup analysis

No subgroup analyses have been explored in the economic analysis.

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B.3.11 Benefits not captured in the QALY calculation

In the current clinical pathway of care, ruxolitinib is the only targeted treatment available and is associated with low response rates, with less than half of participants in clinical trials achieving the primary endpoint.[32,40] In patients who do respond, many will become relapsed or refractory to ruxolitinib over time. In lieu of alternative treatment options, relapsed and refractory patients remain on suboptimal therapy.[23,42] Outcomes in patients no longer responding to ruxolitinib are poor, with a loss of response associated with worse symptoms and an increased spleen size, causing detriments to HRQOL. There is a significant unmet need for a new therapy to address this and provide an alternative treatment option so that clinicians do not have to resort to using limited healthcare resources for suboptimal treatment.

Fedratinib offers a choice for an alternative treatment option for a heterogenous patient population in which each patient responds differently to each treatment, particularly for those with a very poor prognosis who are intolerant and resistant to other treatments and for whom there are no other treatment options.

B.3.12 Validation

Validation of cost-effectiveness analysis

For the development of the cost-effectiveness model, expert clinical and health economic input was sought during the development to ensure that the inputs and assumptions used in the base-case analysis were relevant to UK clinical practice.

Once the model was finalised, technical validation was conducted by health economic modellers. A programmer (other than the one who built the model) reviewed all formulae, code, and labelling in the model. Sensible lower and upper bounds (e.g., £0 for costs, but not negative costs) were input to the model one parameter at a time and the corresponding changes in the results were observed.

The results were checked against their expected impact. For example, setting all AE cost inputs to zero would result in AE cost outputs of £0 across both treatment arms.

SACT data collected during the CDF period provide an opportunity for potential validation of the key data used within the model (i.e., FREEDOM-2 data). SACT data for fedratinib display a more pessimistic OS outcome when compared with FREEDOM-2. However, one-to-one comparison is challenging due to some key differences:

- FREEDOM-2 and SACT differ in terms of study population. The SACT cohort includes older patients, with a median age of 72 years (48% of patients aged 70-79 years and 11% > 80 years). The FREEDOM-2 population was younger, with a median age of 70 years. SACT data display a larger proportion of male versus female patients (76% vs. 56%). Additionally, PS was missing for 48% of the SACT data, making it difficult to compare the disease burden between FREEDOM-2 and the SACT data set.
- Real-world evidence carries higher uncertainty and thus has lower confidence than evidence gathered in a clinical trial setting.
- Median treatment duration in SACT is shorter than median treatment duration in FREEDOM-2. The all-treated fedratinib median treatment duration is 52.5 weeks, whereas in SACT, it is 24.4 weeks. This difference will likely be the source of further uncertainty when comparing OS outcomes between the SACT data set and FREEDOM-2.

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Although treatment duration reported in the SACT data set provides a better reflection of clinical real-word practice, the lack of data for a comparator arm in the SACT data set means that it is not possible to run a scenario based solely on SACT evidence. A scenario that used SACT TTD data in place of FREEDOM-2 TTD data, given the shorter median treatment duration, found that the SACT data set would have produced an overoptimistic result for fedratinib.

B.3.13 Interpretation and conclusions of economic evidence

In FREEDOM-2, fedratinib showed significant improvement in spleen volume response rates compared with BAT. In the cost-effectiveness analysis, fedratinib showed that, although under a conservative assumption of equal OS between fedratinib and BAT, the improved response rate for fedratinib results in an increase of 0.167 QALYs versus BAT. Based on the current simple PASs for fedratinib, approved by the Department of Health, this results in an incremental savings of [redacted] per patient versus BAT; thus, fedratinib dominates BAT. The results were robust for all scenario analyses conducted with only 2 scenarios resulting in increased costs for fedratinib compared with BAT. However, both scenarios resulted in an ICER below £20,000 per QALY. As such, when fedratinib is compared with BAT with the current simple PASs for fedratinib and other treatments at list price, introduction of fedratinib would be cost saving compared with BAT.

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B.5 Appendices

Appendix C. Summary of product characteristics (SmPC) and UK public assessment report

Appendix D. Identification, selection, and synthesis of clinical evidence

Appendix E. Subgroup analysis

Appendix F. Adverse reactions

Appendix G. Published cost-effectiveness studies

Appendix H. Health-related quality-of-life studies

Appendix I. Cost and healthcare resource identification, measurement, and valuation

Appendix J. Clinical outcomes and disaggregated results from the model

Appendix K. Price details of treatments included in the submission

Appendix L. Checklist of confidential information

Appendix M. Supportive materials for the economic evaluation

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund Review

Fedratinib for treating disease-related splenomegaly or symptoms in myelofibrosis (Review of TA756) [ID5115]

Summary of Information for Patients (SIP)

March 2024

Template version	Date amended	Changes since previous version
2.0	Dec 2023	Clarifications made to guidance notes in Section 3i regarding inclusion of statements on cost-effectiveness.

File name	Version	Contains confidential information	Date
ID5115_Fedratinib_NICE_SIP_Final	1.0	No	11 March 2024

Summary of Information for Patients (SIP): The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine

Fedratinib (INREBIC®)

1b) Population this treatment will be used by:

Adults with disease-related splenomegaly or symptoms of:

- Primary myelofibrosis (also known as chronic idiopathic myelofibrosis)
- Post-polycythaemia vera myelofibrosis
- Post-essential thrombocythaemia myelofibrosis

1c) Authorisation

In February 2021, fedratinib for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post-polycythaemia vera myelofibrosis, or post-essential thrombocythaemia myelofibrosis was approved for use in Europe.

1d) Disclosures

BMS currently has 2 multiyear collaborative projects with Macmillan Cancer Support. One is evaluating the value of prehabilitation in cancer care, and the second is the creation of a workforce forecasting tool.

Whilst BMS is not engaged in other collaborative projects, grant funding has been provided to the following patient organisations over the past year: Blood Cancer UK, Cancer52, Leukaemia Care, Lymphoma Action, Maggie's Centres, and Tenovus Cancer Care.

BMS has also contributed to Blood Cancer UK's Blood Cancer Action Plan and has been a stakeholder in Tenovus Cancer Care's Lung Health Check project in Wales.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Myelofibrosis is a rare blood illness characterised by abnormal low levels of blood cells (cytopenias), scarring in the bone marrow (fibrosis), and blood cell production outside the bone marrow (extramedullary haematopoiesis). It often results in an enlarged spleen (splenomegaly); general symptoms that can affect the whole body such as fatigue, fever, weight loss, and night sweats (constitutional symptoms); and a reduced life expectancy.[1-4] The illness can appear as primary myelofibrosis on its own or as a result of the body making too many red blood cells (polycythaemia vera) or when the body produces too many platelets, which are involved in blood clotting (essential thrombocythaemia). In the United Kingdom, approximately 3.2 out of every 100,000 people are living with myelofibrosis at any given time over a 10-year period. There are approximately 0.6 out of every 100,000 people diagnosed with myelofibrosis.[5] This is roughly 2,130 people living with myelofibrosis, half of whom are expected to have severe myelofibrosis (intermediate-2 and high-risk disease).[5]

More than 80% of people with myelofibrosis experience splenomegaly, whilst other signs and symptoms of myelofibrosis include those related to cytopenias (> 35% of people), fatigue (> 90%), and constitutional symptoms (approximately 30%).[6] As the disease progresses, symptoms get worse, which can affect a person's quality of life.[1,2,7] People with primary myelofibrosis who go on to develop acute myeloid leukaemia (AML) (a type of blood cancer where the bone marrow makes too many immature white blood cells, affecting the body's ability to fight infections), they have a life expectancy of 3 to 8 months, and they have only a 5% to 10% chance of being alive 1 year after an AML diagnosis.[8,9]

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Myelofibrosis is diagnosed and categorised by risk using one of the following scoring systems: the International Prognostic Scoring System (IPSS), the Dynamic International Prognostic Scoring System (DIPSS), or the DIPSS Plus.[10] These are used to classify individuals into 1 of 4 risk groups (low, intermediate-1, intermediate-2, and high) based on factors such as age, presence of constitutional symptoms, and haematological measures.

Currently, only ruxolitinib is recommended by NICE for use in patients with intermediate-2 or high-risk disease.[11] When patients become ill following recovery (relapsed), unresponsive or resistant to treatment (refractory), or intolerant to treatment, the introduction of fedratinib to the pathway of care provides an opportunity for a new treatment in a patient group otherwise linked with a short life expectancy. Several published reports of patients who were relapsed, refractory, or intolerant demonstrate a median life expectancy of 13 to 16 months after ruxolitinib treatment.[11-14]

Additional test:

Thiamine levels in the body should be assessed before starting treatment with fedratinib and during treatment as your medical team feels necessary (for example, each month for the first 3 months and every 3 months thereafter). Fedratinib treatment should not be started in individuals with low levels of thiamine.

2c) Current treatment options:

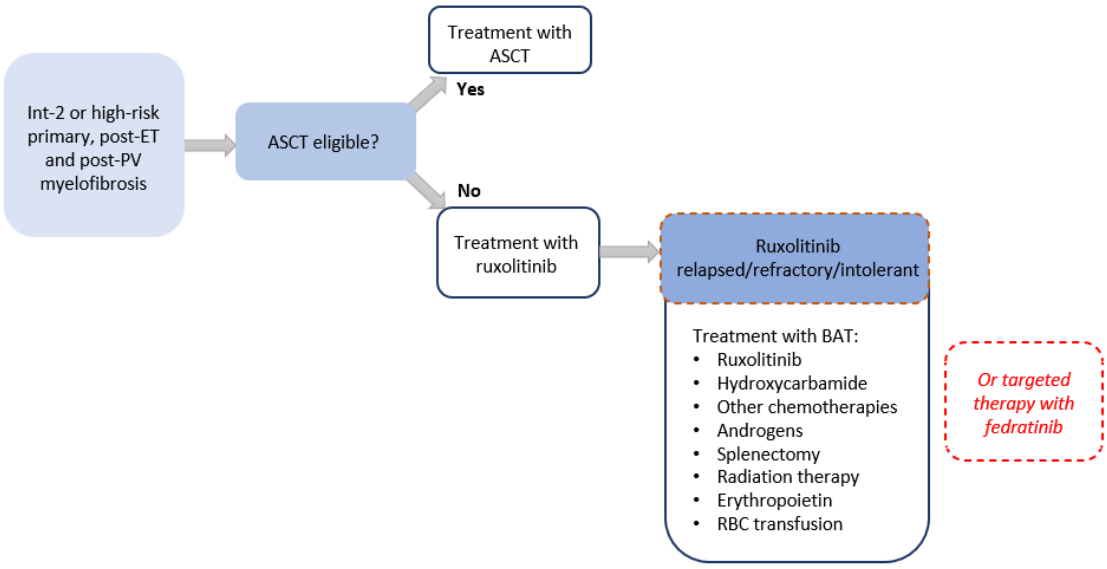
The purpose of this section is to set the scene on how the condition is currently managed:

- *What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.*
- *Please also consider:*
  - *if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.*
  - *are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.*

Allogeneic stem cell transplant (ASCT) is the only possible treatment that can cure myelofibrosis. ASCT is a medical procedure where healthy stem cells from a donor are given to a patient whose own stem cells have been damaged or destroyed. However, it is only suitable for people who are fit enough to go through the treatment because it is linked with the development of other health issues and death.[15] ASCT is usually only considered for people with intermediate-2 or high-risk myelofibrosis, and only 5% to 10% will meet the eligibility criteria for such an intensive therapy.[16,17]

Other treatment options aim to relieve debilitating symptoms, particularly enlarged spleen (splenomegaly) and low levels of blood cells (cytopenia), and improve quality of life. This includes therapies such as ruxolitinib. Ruxolitinib is the only targeted treatment recommended for use in people with myelofibrosis (with intermediate-2 and high-risk disease) in clinical practice in the United Kingdom.[11]

Figure 1. Clinical pathway of care for people with intermediate-2 and high-risk myelofibrosis in England



ASCT = allogenic stem cell transplant; BAT = best available therapy; ET = essential thrombocythaemia; Int = intermediate; PV = polycythaemia vera; RBC = red blood cell.

Ruxolitinib is associated with low response rates: less than half of participants in clinical trials achieved the main goal, which was to reduce symptoms of an enlarged spleen by 35%.[18,19] In patients who do respond, many will become ill following recovery (relapsed) or unresponsive or resistant to treatment (refractory) to ruxolitinib over time. As an alternative to a lack of other treatment options, relapsed and refractory patients remain on suboptimal therapy.[20,21] Patients no longer responding to ruxolitinib have worse symptoms and an increased spleen size, causing detriments to quality of life. Fedratinib fills the gap for an alternative treatment option that provides an important improvement in the signs and symptoms in patients previously treated with ruxolitinib.

2d) Patient-based evidence (PBE) about living with the condition

Context:

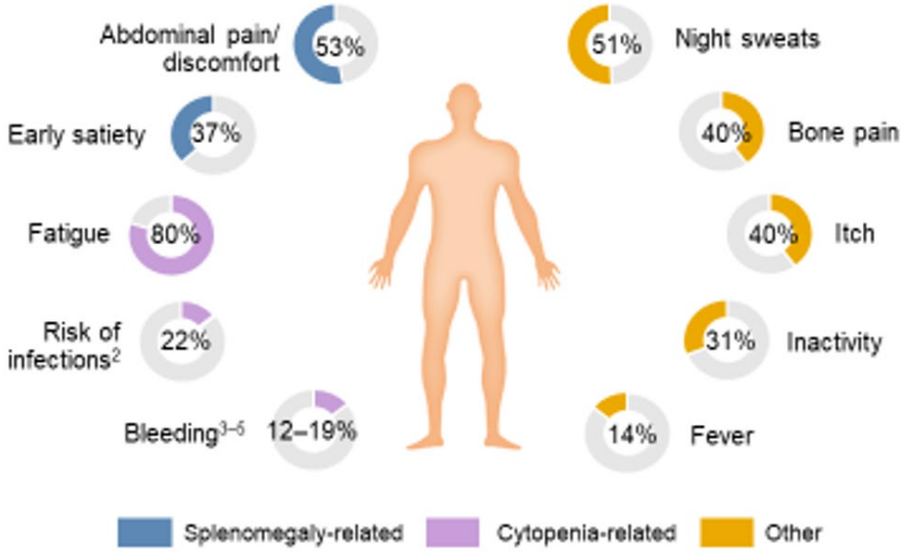
- *Patient-based evidence (PBE) is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.*

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about patient needs and disease experiences. Please include the

methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Myelofibrosis is associated with a range of debilitating symptoms that may worsen as the disease progresses and can affect quality of life.[1,2,7]

Figure 2. Debilitating symptoms of myelofibrosis



Adapted from Mesa et al. (2016)[22]; Polverelli et al. (2015)[23]; Devendra et al. (2017)[24]; Kander et al. (2015)[25]; Finazzi et al. (2012)[26]

In patients who have been treated with ruxolitinib, the physical and psychological burden of myelofibrosis is particularly pronounced. A comparison of quality of life at the beginning of treatment for patients who had never had a Janus kinase (JAK) inhibitor from one of the ruxolitinib trials, COMFORT-II,[27] with starting data for patients who had received ruxolitinib in the fedratinib JAKARTA-2 trial suggested that quality of life is worse in people who have been treated with ruxolitinib. Both studies assessed quality of life using a validated questionnaire called the EORTC QLQ-C30 (see glossary for description). In the FREEDOM-2 trial, quality of life was assessed by another validated questionnaire called the EQ-5D-5L (see glossary for description) in patients previously treated with ruxolitinib who were then treated with fedratinib. The results of the questionnaires showed an important improvement for patients from the start of treatment with fedratinib to the data analysis cutoff date.[28]

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Myelofibrosis is a rare blood illness characterised by abnormally low levels of blood cells (cytopenias), scarring in the bone marrow (fibrosis), and blood cell production outside the bone marrow (extramedullary haematopoiesis). It often results in an enlarged spleen (splenomegaly). The illness can appear as primary myelofibrosis on its own or as a result of the body making too many red blood cells (polycythaemia vera) or when the body produces too many platelets, which are involved in blood clotting (essential thrombocythaemia).

Fedratinib blocks the activation of Janus kinase (JAK) enzymes, which are involved with the production and growth of blood cells. Blocking reduces the abnormal production of blood cells, therefore reducing the size of the spleen and relieving symptoms such as fever, night sweats, bone pain, and weight loss in patients with myelofibrosis.[29,30]

Fedratinib is more effective at blocking the JAK enzymes than ruxolitinib, the current treatment option. Thus, fedratinib is a new treatment to relieve symptoms and improve quality of life whilst extending life in people unable to have treatment with allogenic stem cell transplant.[29,31]

Fedratinib summary of product characteristics and patient information leaflet:

- https://www.ema.europa.eu/en/medicines/human/EPAR/inrebic
- https://www.medicines.org.uk/emc/product/12481/pil#about-medicine
- https://www.medicines.org.uk/emc/product/12481/smpc#about-medicine

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- *Yes / No*

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Response: No

Not applicable.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.
How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Fedratinib is administered orally as a single daily dose of 400 mg (four 100-mg tablets) taken with or without food.

Treatment with fedratinib should be started and monitored under the supervision of physicians experienced in the use of anticancer medicinal products. Testing at the start of treatment should include thiamine (vitamin B1) levels, complete blood count, hepatic panel, amylase/lipase, blood urea nitrogen, and creatinine and should be obtained before starting treatment, periodically during treatment, and as clinically indicated. A change in the amount of fedratinib should be considered for haematologic and non-haematologic toxicities. Fedratinib can be continued until loss of benefit or stopped for patients who are unable to tolerate 200 mg daily of fedratinib.[32,33]

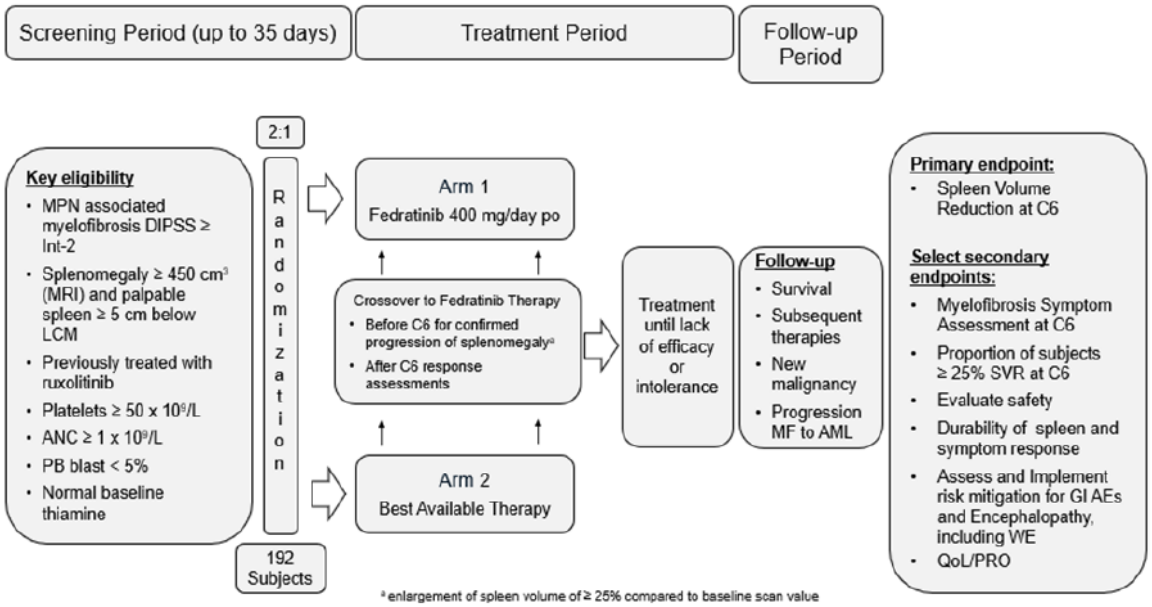
Fedratinib and ruxolitinib are both taken as a tablet that is swallowed and both need blood tests before treatment starts, so are very similar in terms of how the treatment is given.[33,34]

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The key medical study used for this submission is FREEDOM-2, a phase 3, open-label, randomised study of 201 participants (103 sites in 16 countries) with intermediate-2 or high-risk primary myelofibrosis, post-polycythaemia vera myelofibrosis, or post-essential thrombocythaemia myelofibrosis. FREEDOM-2 provides direct evidence for fedratinib in a patient population that has been treated with ruxolitinib (N = 134) and compared with best available treatment (BAT), which included ruxolitinib (52 of 67 participants) and red blood transfusions (19 of 67 participants).[28] The study is still ongoing with an estimated completion date of 23 June 2025; however, the clinical cut-off date for data in this submission was 27 December 2022.

Figure 3. FREEDOM-2: study design



AE = adverse event; AML = acute myeloid leukaemia; ANC = absolute neutrophil count; C6 = cycle 6; DIPSS = Dynamic International Prognostic Scoring System; GI = gastrointestinal; Int-2 = intermediate-2; LCM = left costal margin; MF = myelofibrosis; MPN = myeloproliferative neoplasm; MRI = magnetic resonance imaging; PB = peripheral blood; po = orally; PRO = patient-reported outcome; QoL = quality of life; SVR = spleen volume reduction; WE = Wernicke's encephalopathy.

Source: BMS data on file (2023)[28]

Real-world evidence:

The Systemic Anti-Cancer Therapy (SACT) data set was an evaluation of real-world treatment effectiveness of fedratinib in the Cancer Drugs Fund (CDF) population. There were 54 participants treated with 400 mg fedratinib, previously treated with ruxolitinib and with a current diagnosis of intermediate-2 or high-risk primary myelofibrosis, post-polycythaemia vera myelofibrosis, or post-essential thrombocythaemia myelofibrosis. The study period in the CDF was 14 months, from November 2021 to January 2023.[32] This study was not included in the economic model because it does not report all the key goals, and does not compare fedratinib with BAT.

Previous trials:

JAKARTA was a randomised, double-blind, placebo-controlled, phase 3 trial that compared 400 mg (N = 96) or 500 mg (N = 97) fedratinib with placebo (N = 96) in participants with intermediate-2 or high-risk primary myelofibrosis, post-polycythaemia vera myelofibrosis, or post-essential thrombocythaemia myelofibrosis with enlarged spleen (splenomegaly). Completion date of the study was June 2014. The study is not relevant to this submission and is not included in the main dossier because there was a lack of similarities to FREEDOM-2 trial and the patient group was unexposed to ruxolitinib.[35]

JAKARTA-2 was a phase 2, multicentre, open-label, single-arm study that evaluated the efficacy of a once daily, 400 mg dose of fedratinib in 97 participants previously treated

with ruxolitinib and was included in the original NICE technology appraisal assessment of fedratinib (TA756). The study was completed in April 2014. JAKARTA-2 has not been used to populate the model for this submission.[36]

FREEDOM was a phase 3, single-arm, United States–based, open-label study of 38 participants previously treated with ruxolitinib and with intermediate-2 or high-risk primary myelofibrosis, post-polycythaemia vera myelofibrosis, or post-essential thrombocythaemia myelofibrosis. This study was not included in the economic model because it did not include a compatible patient group. The study was completed in November 2023.

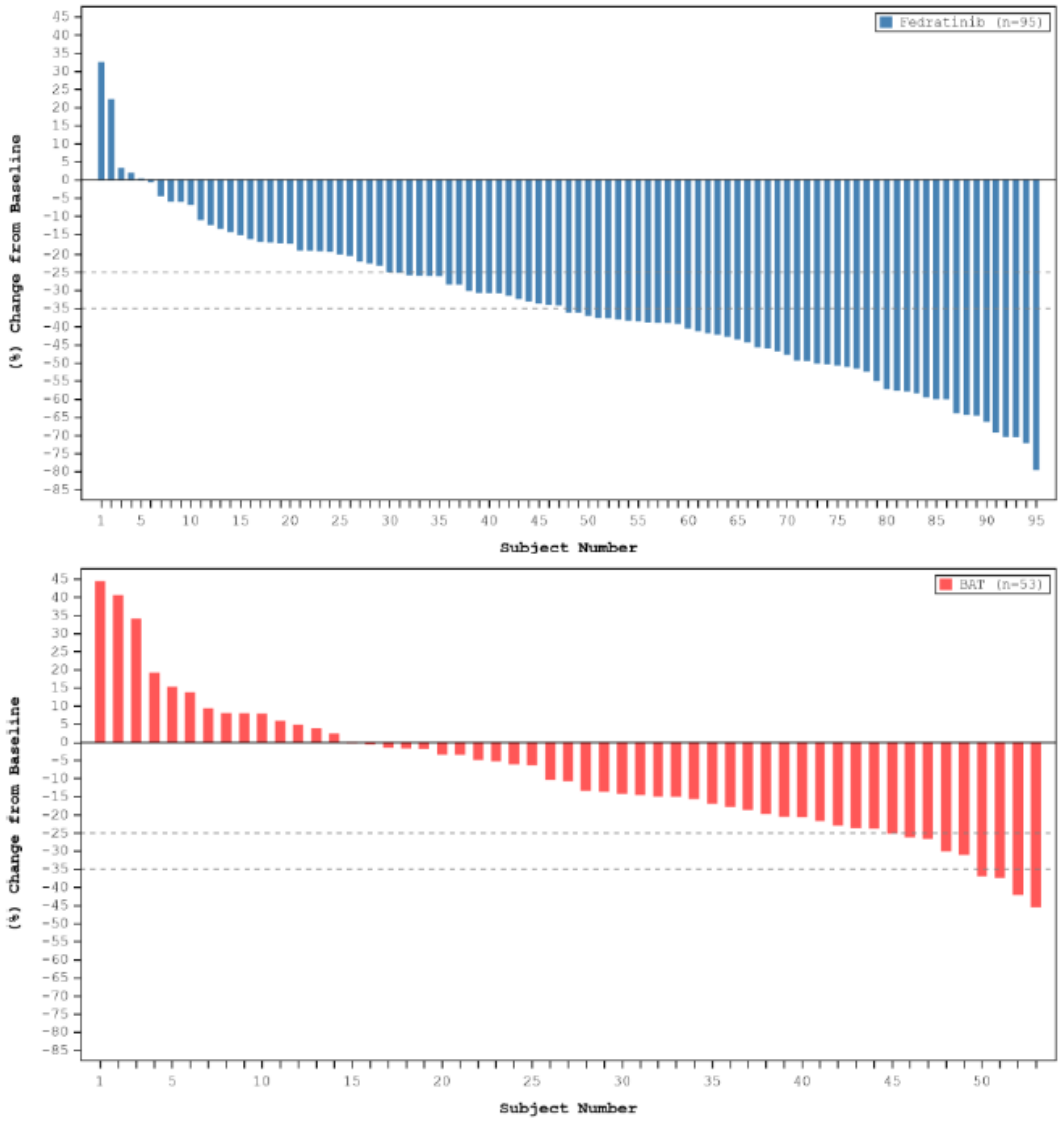
3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.
In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

The efficacy of fedratinib over BAT in patients who have been treated with ruxolitinib has been demonstrated in FREEDOM-2[28] and is supported by similar efficacy in the FREEDOM trial, the JAKARTA-2 trial, and the JAK inhibitor–unexposed patient group from JAKARTA.[35,36]

The main goal in the FREEDOM-2 clinical trial was spleen volume response rate, defined as ≥ 35% spleen volume reduction (SVR) at the end of cycle 6 (EOC6). 35.8% of participants receiving fedratinib and 6% receiving BAT achieved a ≥ 35% SVR (Figure 4).[28] Figure 4 shows the change in spleen volume at EOC6 compared with at the start of the study (baseline). Each bar represents a participant. The first figure (in blue) is the fedratinib group, and the second figure (in red) is the BAT group. In the fedratinib group in the first figure, only 5 participants had no reduction in spleen volume (change above 0), while most participants did have a reduction in spleen volume (change below 0). In the BAT group in the second figure, 14 patients had no reduction in spleen volume.

Figure 4. FREEDOM-2: percentage change in spleen volume from baseline to EOC6 in participants with MRI/CT scan at EOC6 (ITT population)



BAT = best available therapy; CT = computed tomography; EOC6 = end of cycle 6; ITT = intention to treat; MRI = magnetic resonance imaging.

Note: Each bar represents a participant with both baseline and post-baseline results. The dotted lines represent the 25% and 35% change from baseline.

Source: BMS data on file (2023)[28]

The secondary goal in the FREEDOM-2 clinical trial was symptom response rate defined as ≥ 50% reduction in Total Symptom Score (TSS) at EOC6. 34.1% of participants receiving fedratinib and 16.9% receiving BAT achieved a ≥ 50% reduction in TSS. An additional secondary goal of spleen response rate defined as ≥ 25% SVR at EOC6 was achieved in 47% of participants receiving fedratinib and 13.4% receiving BAT.[37]

The results of the main goal (≥ 35% SVR at EOC6), as well as the results for both of the 2 key secondary goals (≥ 50% reduction in TSS at EOC6, ≥ 25% SVR at EOC6), proved superiority for fedratinib over BAT in FREEDOM-2.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

*Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs)**.*

Please include any patient preference information (PPI) relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Changes in quality of life, as reported by patients themselves, were measured in the FREEDOM-2 trial by validated and routinely used questionnaires.

In EQ-5D-5L questionnaires, for the visual analogue scale (see glossary for description of these) results, both fedratinib and BAT treatment groups had increases from baseline in mean scores, indicating improvement during the treatment period. The fedratinib group showed an important improvement at cycle 2 through cycle 5. The BAT group had no timepoints with important improvements. For the utility scores, the fedratinib and BAT groups showed important improvements by increases from starting mean scores, indicating improvement during the treatment period.[28]

In EORTC QLQ-C30 questionnaires, both fedratinib and BAT treatment groups had important improvements in quality of life by increases from starting mean scores for global health status.[28]

Thus, fedratinib is considered to have an impact on the quality of life of patients with intermediate-2 or high-risk primary myelofibrosis, post-polycythaemia vera myelofibrosis, or post-essential thrombocythaemia myelofibrosis.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

The safety results of FREEDOM-2 were similar with the known safety record of fedratinib. The approaches for avoiding gastrointestinal and thiamine-related toxicities generally worked.[28] Overall, 50% of the fedratinib group completed 12 cycles of treatment, whilst only 10% of the BAT group completed 12 cycles, suggesting overall tolerability of fedratinib. Furthermore, patients in the fedratinib group were on treatment longer than patients in the BAT group, which may lead to more adverse events. Treatment-emergent

adverse events are any unwanted or negative effects that appear after starting a treatment. The most common treatment-emergent adverse events by study arm were as follows (number of participants [%])[28]:

- Fedratinib group: diarrhoea (62 [46.3%]), anaemia (59 [44%]), nausea (54 [40.3%])
- Fedratinib crossover group: anaemia (20 [43.5%]), diarrhoea (17 [37%]), thrombocytopenia (13 [28.3%])
- BAT group: anaemia (24 [35.8%]), asthenia (16 [23.9%]), thrombocytopenia (12 [17.9%])

The most common treatment-related adverse events by study arm were as follows (number of participants [%])[28]:

- Fedratinib group: diarrhoea (54 [40.3%]), nausea (45 [33.6%]), thrombocytopenia (32 [23.9%])
- Fedratinib crossover group: diarrhoea (15 [32.6%]), anaemia (14 [30.4%]), nausea (11 [23.9%])
- BAT group: anaemia (9 [13.4%]), thrombocytopenia (4 [6%]), constipation (3 [4.5%])

Fedratinib summary of product characteristics:

- https://www.ema.europa.eu/en/medicines/human/EPAR/inrebic
- https://www.medicines.org.uk/emc/product/12481/smpc#about-medicine
- https://www.medicines.org.uk/emc/product/12481/pil#about-medicine

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- *Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.*
- *Please include benefits related to the mode of action, effectiveness, safety and mode of administration*

Fedratinib provides an alternative treatment option for patients previously treated with ruxolitinib, providing improved patient outcomes. Specifically, the FREEDOM-2 study demonstrated that treatment with fedratinib is associated with considerable reductions in spleen volume and size, as well as improvements to symptoms in participants previously treated with ruxolitinib, compared with BAT.

Key benefits from FREEDOM-2:

- Enlarged spleen (splenomegaly) is the key physical feature and cause of symptoms of myelofibrosis. As such, SVR forms an important treatment goal. Internationally recognised research groups have identified ≥ 35% SVR as the appropriate threshold for defining response in patients with myelofibrosis.[38] Approximately a third of participants on fedratinib in FREEDOM-2 (35.8%) achieved this response, in comparison to 6% of participants on BAT in FREEDOM-2.[28,39] This demonstrates that fedratinib reduces symptoms associated with an enlarged spleen.
- As an alternative to a lack of other treatment options, the relief of debilitating symptoms is another important treatment goal in myelofibrosis. The important improvement for symptom response is ≥ 50% reduction in TSS,[38] with 34.1% of participants on fedratinib in FREEDOM-2 having achieved this, compared with 16.9% of participants on BAT in FREEDOM-2.[28,39] Improving these symptoms provides patients with an improved ability to carry out normal daily functions and relieves some of the physical and psychological burden associated with myelofibrosis. The improvement of these symptoms maintains quality of life for people with myelofibrosis.
- The safety analysis of fedratinib in FREEDOM-2 revealed no new safety concerns, and symptoms are considered manageable for people with myelofibrosis.

The proposed position of fedratinib in the treatment pathway is narrower than the marketing authorisation because the population of patients who have been treated with ruxolitinib represents the greatest unmet need in myelofibrosis, for which the clinical and cost-effectiveness of fedratinib is most demonstrable. The life expectancy in patients who have been treated with ruxolitinib is poor, with studies indicating a median overall survival of 13 to 16 months following ruxolitinib discontinuation.[11-14] Furthermore, should fedratinib be included in the current treatment landscape in NHS England, additional treatment options would be available for the patient group with myelofibrosis.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- *Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?*
- *Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration*
- *What is the impact of any disadvantages highlighted compared with current treatments*

Over the full course of the FREEDOM-2 study (full treatment period + crossover treatment period + follow-up period), the proportion of deaths was similar for the fedratinib group and the BAT group.[28,37,40] There are clear methodological issues that may result in an underestimate of overall survival for the fedratinib group, which means that the overall survival data need to be considered with caution. In the group that received BAT, nearly

70% did cross over to fedratinib, leaving very few participants in the BAT-only group, something the study was not prepared for.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- *The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)*
- *If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?*
- *How the condition, taking the new treatment compared with current treatments affects your quality of life.*

As part of the appraisal process, NICE ask that manufacturers submit an economic analysis, showing whether the new treatment is worth the costs to the NHS in terms of its benefits (effects). This is usually done using a cost-effectiveness model. In the model, benefits are measured in quality-adjusted life-years (QALYs), which are a unit of measurement equal to 1 year of life in perfect health and are shown in relation to the change in costs to the NHS caused by the new treatment being used.

The current submission includes such a cost-effectiveness analysis comparing fedratinib with current BAT. The model uses the data from the FREEDOM-2 trial to model how fedratinib and BAT lead to different proportions of patients responding to treatment but also how this could affect patient survival. The model considered factors such as the costs of the medicines, the costs of treating side effects, the costs of other healthcare services, and the quality of life of the patients. The results of the cost-effectiveness analysis show that treatment with fedratinib leads to improvements in quality of life whilst at the same time is likely to save money for the NHS.

The main uncertainties of the model are related to the effect of crossover, which means that some patients in the trial who were given BAT switched to fedratinib later on, either because their spleen got worse or they were allowed to switch after 24 weeks of BAT, according to the trial recommendations. This may have reduced the observed differences between fedratinib and BAT in the trial and specifically made it harder to estimate the true effect of fedratinib on survival. Several methods were used to try to adjust for the crossover, but they all had limitations and were not scientifically valid. Therefore, the model may have undervalued the benefits and costs of fedratinib compared with BAT.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations. *If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)*
Current treatments within the clinical pathway for people with myelofibrosis are limited and associated with low response rates. Fedratinib offers an alternative treatment option for people no longer responding to ruxolitinib, the only treatment currently approved. The FREEDOM-2 study showed that treatment with fedratinib, compared with BAT, is associated with considerable reductions in spleen volume and size, as well as marked improvements to symptoms in individuals previously treated with ruxolitinib. In the cost-effectiveness analysis, the improved response rate for fedratinib results in an increase of 0.167 QALYs (see glossary for description) compared with BAT. Based on the current simple patient access schemes for fedratinib, approved by the Department of Health, this resulted in a cost saving per patient versus BAT, thus fedratinib dominates (is cheaper and better than) BAT.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. *Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics* *More information on how NICE deals with equalities issues can be found in the NICE equality scheme* *Find more general information about the Equality Act and equalities issues here*
No equality issues are anticipated.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. *Where possible, please provide open access materials or provide copies that patients can access.*

Further information on trial data supporting fedratinib in primary myelofibrosis, post-polycythaemia vera myelofibrosis, or post-essential thrombocythaemia myelofibrosis can be found here:

- Original NICE technology appraisal: https://www.nice.org.uk/guidance/ta756
- FREEDOM-2 trial: https://www.clinicaltrials.gov/study/NCT03952039
- FREEDOM trial: https://www.clinicaltrials.gov/study/NCT03755518
- JAKARTA-2 trial: https://www.clinicaltrials.gov/study/NCT01523171
- JAKARTA trial: https://www.clinicaltrials.gov/study/NCT01437787
- JAKARTA-2 publications:
  - Harrison CN, Schaap N, Vannucchi AM, Kiladjian J-J, Tiu RV, Zachee P, et al. Janus kinase-2 inhibitor fedratinib in patients with myelofibrosis previously treated with ruxolitinib (JAKARTA-2): a single-arm, open-label, non-randomised, phase 2, multicentre study. Lancet Haematol. 2017;4(7):e317-24. doi:10.1016/S2352-3026(17)30088-1.
  - Harrison C, Schaap N, Vannucchi A, Kiladjian J-J, Jourdan E, Silver R, et al. Fedratinib in patients with myeloproliferative neoplasm-associated myelofibrosis previously treated with ruxolitinib: a reanalysis of the phase 2 JAKARTA-2 study. Presented at 24th European Hematology Association (EHA) Congress; 13-16 June 2019. Amsterdam, Netherlands.
  - Harrison CN, Mesa RA, Jamieson C, Hood J, Bykowski J, Zuccoli G, Brewer J. Case series of potential Wernicke's encephalopathy in patients treated with fedratinib. Blood. 2017;130(Suppl 1):4197. doi:10.1182/blood.V130.Suppl_1.4197.4197.
  - Harrison CN, Schaap N, Vannucchi AM, Kiladjian JJ, Jourdan E, Silver RT, et al. Fedratinib in patients with myelofibrosis previously treated with ruxolitinib: an updated analysis of the JAKARTA2 study using stringent criteria for ruxolitinib failure. Am J Hematol. 2020;95(6):594-603. doi:10.1002/ajh.25777.
  - Pardanani A, Harrison C, Cortes JE, Cervantes F, Mesa RA, Milligan D, et al. Safety and efficacy of fedratinib in patients with primary or secondary myelofibrosis: a randomized clinical trial. JAMA Oncol. 2015 Aug;1(5):643-51. doi:10.1001/jamaoncol.2015.1590.
- European Medicines Agency (EMA) website: https://www.ema.europa.eu/en/medicines/human/EPAR/inrebic
- Summary of product characteristics: https://www.medicines.org.uk/emc/product/12481/smpc#about-medicine
- The diseases area:
  - https://www.mpnvoice.org.uk/about-mpns/questions/myelofibrosis-mf/

- https://www.macmillan.org.uk/cancer-information-and-support/blood-cancer/myelofibrosis-mf
- https://www.youtube.com/watch?v=nMxWLC6X2ds&t=72s

Further information on NICE and the role of patients**:**

- Public Involvement at NICE: https://www.nice.org.uk/about/nice-communities/nice-and-the-public/public-involvement
- NICE's guides and templates for patient involvement in health technology assessments: https://www.nice.org.uk/about/nice-communities/nice-and-the-public/public-involvement/support-for-vcs-organisations/help-us-develop-guidance/guides-to-developing-our-guidance
- European Federation of Pharmaceutical Industries and Associations (EFPIA) – Working Together With Patient Groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- International Network of Agencies for Health Technology Assessment (INAHTA): http://www.inahta.org
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Term	Definition / explanation
AE	Adverse event
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
ASCT	Allogeneic stem cell transplant
BAT	Best available therapy
BMS	Bristol Myers Squibb
CDF	Cancer Drugs Fund, a period of managed access, supported by additional data collection to answer the clinical uncertainty
CT	Computed tomography
DIPSS	Dynamic International Prognostic Scoring System
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EOC6	End of cycle 6

EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Quality of Life of Cancer Patients (Core 30)
EQ-5D index and EQ-5D visual analogue scale (VAS)	The EQ-5D instrument records the patient's self-rated health by assessing 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels that patients can choose (for example, I have no problems with self-care; I have some problems washing or dressing myself; I am unable to wash or dress myself). A patient will tick the most appropriate level for each of the 5 dimensions. Based on this, the EQ-5D index assigns patients a single value measuring the patient's self-rated health status (the index), whereas the visual analogue scale records health status on a graduated (0-100) scale, with higher scores representing a higher quality of life.
ET	Essential thrombocythaemia
GI	Gastrointestinal
Health economic model	Tool to compare the costs and benefits of alternative interventions, treatments, or policy options
HTAi PCIG	Health Technology Assessment International – Patient & Citizens Involvement Group
IJTAHC	*International Journal of Technology Assessment in Health Care*
INAHTA	International Network of Agencies for Health Technology Assessment
IPSS	International Prognostic Scoring System
ITT	Intention to treat
JAK	Janus kinase
LCM	Left costal margin
MF	Myelofibrosis
MPN	Myeloproliferative neoplasm
MRI	Magnetic resonance imaging
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
Overall survival	Death from any cause
PB	Peripheral blood
PRO	Patient-reported outcome
PV	Polycythaemia vera
QALY	Quality-adjusted life-year, a measure of health outcomes that considers length and quality of life
QoL	Quality of life
RBC	Red blood cell
SIP	Summary of Information for Patients
SVR	Spleen volume reduction
TSS	Total symptom score
WE	Wernicke's encephalopathy

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

Response:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Fedratinib for treating disease-related splenomegaly or symptoms in myelofibrosis (Review of TA756) [ID5115]

Clarification questions

March 2024

File name	Version	Contains confidential information	Date
		Yes/no	27/03/2024

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Decision problem

A1. PRIORITY Momelotinib is a comparator listed in the NICE scope with the caveat that it was "*subject to NICE evaluation*" at the time the scope was finalised. However, we note that positive final guidance has now been released and therefore the committee may wish to see a comparison against momelotinib. Please provide an updated systematic literature review (SLR) that identifies relevant studies to allow comparison against momelotinib and, if relevant, an indirect treatment comparison.

Response: The technology appraisal guidance of momelotinib (TA957) was published 20 March 2024; therefore, it cannot be considered as established NHS clinical practice in England and Wales as described in the NICE methods guide. Thus, we have not considered momelotinib as a relevant comparator. Further, the licensed indication for momelotinib is not aligned with the licensed indication of fedratinib. Momelotinib should only be administered to patients with moderate to severe anaemia, whereas fedratinib does not have a restriction based on the level of anaemia. Fedratinib has been proven to be effective regardless of the patient's status of anaemia. A potential future overlap of this subset of the fedratinib population is possible but equates to a very small absolute number of patients. An

analysis of such limited patient numbers introduces uncertainty, without the possibility of drawing a reliable conclusion, as well as requiring significant resources, which does not align with BMS current business priorities. Clinicians and the available data consistently support the use of ruxolitinib as the entrenched standard of care, where fedratinib provides a requested treatment alternative for the full patient population and is favoured over best available therapy (BAT) across subgroups.

A2. The scope describes *"established clinical practice*" as a comparator for "*For people whose disease was previously treated with ruxolitinib or if ruxolitinib is not appropriate (including people with low or intermediate-1 risk disease)*". Please confirm that the company's positioning of fedratinib is for patients who have been treated with ruxolitinib, and therefore the company submission (CS) does not address the clinical or cost-effectiveness of fedratinib in patients in whom ruxolitinib is not appropriate (including people with low or intermediate-1 risk disease).

Response: Correct. This submission focusses on the same population outlined in TA756.

Literature searches: Clinical SLR

A3. CS Appendices, Section D.1.1, page 4, Table 1. The table of databases and information sources searched indicates that searches were conducted on ClinicalTrials.gov. Was the WHO International Clinical Trials Registry Platform (ICTRP) also searched?

Response: No. This was not searched in the original submission. This will not impact the key results.

A4. CS, Appendices, Section D.1.1.1, page 5, Table 2 (also applies to updated searches in D.1.1.2., Table 5, and D.1.1.3., Table 8). Search terms have been used to identify studies of the types eligible for inclusion in the review (randomised controlled trials [RCTs], non-RCTs and real-world evidence); however there is no indication that these are based on published filters which have been validated for

sensitivity/precision in identifying eligible studies. Please indicate whether this was the case (providing a supporting citation to relevant validation studies).

Response: The company used search terms to restrict the evidence base to RCTs and non-RCTs, and observational or single arm studies based on filters which have been adapted from those developed by the Scottish Intercollegiate Guidelines Network (SIGN)[1]. SIGN collaborates with NICE in guideline development work.

A5. CS, Appendices, Section D.1.2., page 14. Table 11. The search strategies for Medline and Embase (tables 2, 5, 8) show in their final lines that an English language limit was applied. Given the dangers of language bias, please provide a justification for the decision to apply this limit and, in particular, for doing so at the searching rather than screening/reviewing stage.

Response: The English language is widely used for publication purposes and is the relevant language for submissions to NICE. Therefore, applying such a limit at the search stage ensures an efficient and precise strategy.

A6. CS, Appendices, Section D.1.1.1., page 5, Table 2 (also applies to updated searches in D.1.1.2., Table 5, and D.1.1.3., Table 8). These searches appear to have been performed simultaneously for two databases (MEDLINE and Embase) but without changing the subject headings (MeSH or Emtree as appropriate) to suit each database. Please comment on the possible implications for retrieval.

Response: Using different MeSH terms between the 2 databases would not yield a significant difference from the results presented in the appendices. This is because Medline and Embase use a similar syntax and are both on the Ovid database. References that may have been lost could also be found and retrieved from other databases, as PubMed, EBSCO and the Cochrane database were also searched.

A7. CS, Appendices, Section D.1.1.1., page 5, Table 2 (also applies to updated searches in D.1.1.2., Table 5, and D.1.1.3., Table 8). For the Intervention search terms, drug names have been searched in titles, abstracts and subject headings, but not in other specialist fields ('name of substance'.nm in MEDLINE and 'drug trade

[1] https://www.sign.ac.uk/what-we-do/methodology/search-filters/

name'.tn in Embase). Please explain the reasoning behind this decision and comment on the possible implications for retrieval.

Response: The intervention and comparator terms were searched using a mix of both free-text search terms and Emtree/MeSH terms, which removes the possibility of missing relevant studies.

Clinical effectiveness: Trials and data availability

A8. PRIORITY CS Section B.2.1 states that the clinical SLR has not been updated since February 2020 because no additional drugs have been approved by NICE since this date, therefore no additional evidence is expected other than the FREEDOM-2 trial.

a) Please confirm that no further trials of fedratinib or other relevant interventions in the relevant population have been published since this date.

b) Please state what steps the company has taken to be sure that this is the case.

Response:

a) There are no further trials of fedratinib or other relevant interventions for patients with intermediate-2 or high-risk myelofibrosis previously treated with ruxolitinib that have been published since February 2020, apart from FREEDOM-2, which is still ongoing.

b) BMS has regularly monitored and reviewed the NICE website for any updates related to drug approvals, guidelines, and evidence. Furthermore, BMS has searched for new publications, clinical trial results, relevant recommendations, as well as collaborated with key experts in the field of myelofibrosis and haematological oncology in order to keep up to date on any emerging evidence. We do acknowledge that momelotinib has very recently been approved by NICE in a population with potential for overlap in a small subset of the population in the indication of fedratinib, which equates to a very small absolute number of patients. However, we do not think this would be considered a relevant comparator for the reasons outlined in A1 because the indication of fedratinib is not restricted based on the level of anaemia, instead

it has been proven to be effective regardless of the anaemic status of the patient.

A9. CS Appendix D.1 provides inclusion criteria for a broader systematic review which identified 247 studies. Appendix D.1.3.1 (Table 12) then lists three included studies "*relevant to the UK setting*". These were: JAKARTA-2, PERSIST-2 and SIMPLIFY-2.

a) The CS Section B.2.1 lists two studies of fedratinib identified from the SLR (JAKARTA and JAKARTA-2) and three studies of fedratinib reported since the SLR (FREEDOM, FREEDOM-2 and Systemic Anti-Cancer Therapy [SACT]). Please explain the inconsistency between the 'included' studies listed in the CS and the 'included' studies listed in Appendix D.1.3.

b) Please provide the narrower inclusion/exclusion criteria relevant to this appraisal.

c) Please confirm which studies meet the inclusion criteria for this appraisal, i) from the search up to February 2020 and ii) for all dates.

d) If further studies meet the inclusion criteria for this appraisal, in addition to the studies listed in (a), please provide them.

Response:

a) The inconsistency between the studies listed in the clinical summary (CS) and those in Appendix D.1.3 arises from the different purposes these lists serve. Appendix D.1.3.1 Table 12 refer to the SLR and the studies relevant for the original TA756 appraisal. These studies are included for information purposes and are not necessarily used for decision-making for this appraisal. Since the publication of TA756, data have become available for FREEDOM and FREEDOM-2 and are presented in the CS. Specifically, the FREEDOM-2 trial is more relevant than JAKARTA-2 for the current appraisal, as it provides the latest data on fedratinib efficacy and safety.

b) The CS provides an overview of studies relevant to this appraisal. A narrower inclusion/exclusion criterion has not been applied for this appraisal.

c) FREEDOM and FREEDOM-2 replace JAKARTA and JAKARTA-2 because these trials provide the most current head-to-head data on fedratinib efficacy and safety in the UK setting.

   i. Up to February 2020:

      - JAKARTA-2: Relevant for the original appraisal but replaced by FREEDOM trials.
      - PERSIST-2 and SIMPLIFY-2: Included in Appendix D.1.3 for information purposes.

   ii. For All Dates:

      - FREEDOM and FREEDOM-2: These trials provide the most current head-to-head data on fedratinib efficacy and safety
      - Systemic Anti-Cancer Therapy (SACT): Also included in the CS.

d) There are no further studies to include.

A10. Please state whether a journal publication of the FREEDOM-2 trial is available or will be available soon.

Response: There are no plans to publish at this stage.

A11. CS Table 3 states that the data cut for the FREEDOM-2 study is Dec 2022. Please describe the pre-planned data cuts for this study and confirm that there are no more recent data cuts available. Please also provide the timings of any future planned data cuts.

Response: No further data cuts are planned in the next 12 months.

A12. PRIORITY CS Table 5 states that patients in FREEDOM-2 could not receive any other drug treatment for their disease whilst on the study.

a) Please clarify if this restriction relates only to the fedratinib arm?

b) Please describe what drug treatments were allowed and disallowed within the best available therapy (BAT) arm.

c) Please clarify if patients in the BAT arm were required to remain on the same drug treatment until treatment discontinuation or crossover. Or could patients receive more than one sequential BAT treatment?

d) Please clarify if patients were able to have a combination of drug treatments as part of BAT.

e) Please provide a breakdown of the drug treatments actually received within BAT (e.g., n/N for each treatment received), including the proportion receiving no treatment (if this was allowed).

Response:

a) Correct. The restrictions only apply to patients randomly assigned to the fedratinib arm or for patients who crossed over to fedratinib treatment.

b) During the study, supportive care for side effects from trial treatments or disease progression, such as antiemetic medications, was allowed to be administered at the discretion of the Investigator. For patients on the BAT arm not crossing over to fedratinib, fedratinib was specifically excluded during the study. Additional treatments may have been prohibited according to the BAT prescribing used.

c) Patients in the BAT arm were not required to remain on the same drug treatment until treatment discontinuation or crossover. If clinically justified, a participant who needs to discontinue BAT treatment can stay on “no treatment” or symptom-directed treatment until crossover as described above or at latest till completion of cycle 6.

d) Correct. A combination of treatments was allowed.

e) A total of 67 patients were randomly assigned to the BAT arm. Table 1 presents the treatment summary for BAT patients in FREEDOM-2.

Table 1. FREEDOM-2: BAT treatment summary

Treatment	BAT (N = 67)
By individual BAT option[a]	
Ruxolitinib	[redacted]
RBC Transfusion	[redacted]
Hydroxyurea	[redacted]
No Treatment	[redacted]
Danazol	[redacted]
Hydroxycarbamide	[redacted]
Interferon	[redacted]
Mercaptopurine	[redacted]
Methylprednisolone	[redacted]
Prednisolone	[redacted]
Prednisone	[redacted]
Thalidomide	[redacted]
By aggregated group	
Ruxolitinib[b]	[redacted]
Hydroxyurea[c]	[redacted]
Ruxolitinib + Hydroxyurea[d]	[redacted]
Other	[redacted]

[a] A participants may be counted in multiple lines, if more than 1 option was taken as BAT.

[b] Participants who ever take ruxolitinib as BAT (either alone or with other medications/RBC transfusion) are included, excluding those who received ruxolitinib and hydroxyurea.

[c] Participants who ever take hydroxyurea as BAT (either alone or with other medications/RBC transfusion) are included, excluding those who received hydroxyurea together with ruxolitinib.

[d] Participants who ever received ruxolitinib and hydroxyurea (with or without extra medications/RBC transfusion) as BAT are included.

A13. In CS Table 1, BAT is described as including splenectomy, radiation therapy and red blood cell (RBC) transfusion. Please provide details of any non-pharmacological treatments that were allowed during the FREEDOM-2 trial and summarise their usage within each trial arm.

Response: There were no restrictions on non-pharmacological treatments in the FREEDOM-2 trial. Table 2 presents the concomitant operations and procedures in FREEDOM-2.

Table 2. FREEDOM-2: concomitant operations and procedures

System organ class preferred term[a]	Fedratinib (N = 134)	BAT (N = 67)
Participants with at least 1 concomitant surgery or procedure[b]	77 (57.5)	40 (59.7)
Surgical and medical procedures	38 (28.4)	22 (32.8)
Appendicectomy	4 (3.0)	2 (3.0)
Bladder catheterisation	4 (3.0)	2 (3.0)
Cataract operation	3 (2.2)	2 (3.0)
Tooth extraction	3 (2.2)	2 (3.0)
Cancer surgery	2 (1.5)	2 (3.0)
Skin lesion removal	3 (2.2)	1 (1.5)
Cholecystectomy	2 (1.5)	1 (1.5)
Enema administration	3 (2.2)	0
Physiotherapy	0	3 (4.5)
Skin neoplasm excision	2 (1.5)	1 (1.5)
Abdominal cavity drainage	2 (1.5)	0
Central venous catheterisation	1 (0.7)	1 (1.5)
Dialysis	2 (1.5)	0
Inguinal hernia repair	1 (0.7)	1 (1.5)
Mechanical ventilation	0	2 (3.0)
Specialist consultation	2 (1.5)	0
Stent placement	2 (1.5)	0
Urethrotomy	1 (0.7)	1 (1.5)
Atrial appendage closure	1 (0.7)	0
Bladder catheter removal	1 (0.7)	0
Blood volume expansion	0	1 (1.5)
Bone marrow transplant	0	1 (1.5)
Bursa removal	1 (0.7)	0
Cardioversion	1 (0.7)	0
Catheter placement	0	1 (1.5)
Cautery to nose	0	1 (1.5)
Colectomy	1 (0.7)	0
Coronary arterial stent insertion	0	1 (1.5)
Craniectomy	1 (0.7)	0
Debridement	1 (0.7)	0
Dental care	1 (0.7)	0
Dermabrasion	1 (0.7)	0
Drain placement	1 (0.7)	0
Duodenal ulcer repair	0	1 (1.5)
Endodontic procedure	1 (0.7)	0
Fluid replacement	1 (0.7)	0

System organ class preferred term[a]	Fedratinib (N = 134)	BAT (N = 67)
Gastrointestinal tube insertion	1 (0.7)	0
Haemodialysis	1 (0.7)	0
Haemorrhoid operation	1 (0.7)	0
Haemostasis	1 (0.7)	0
Influenza immunisation	0	1 (1.5)
Kinesitherapy	1 (0.7)	0
Mass excision	1 (0.7)	0
Meniscus operation	1 (0.7)	0
Muscle operation	0	1 (1.5)
Oesophageal variceal ligation	1 (0.7)	0
Photocoagulation	0	1 (1.5)
Positive airway pressure therapy	0	1 (1.5)
Radiotherapy	1 (0.7)	0
Radiotherapy to spleen	0	1 (1.5)
Removal of foreign body	0	1 (1.5)
Retinal laser coagulation	1 (0.7)	0
Splenectomy	1 (0.7)	0
Splint application	0	1 (1.5)
Suture insertion	0	1 (1.5)
Therapeutic aspiration	0	1 (1.5)
Tonsillectomy	1 (0.7)	0
Transfusion	1 (0.7)	0
Tumour excision	1 (0.7)	0
Vasopressive therapy	0	1 (1.5)
Venous ligation	1 (0.7)	0
Vitrectomy	1 (0.7)	0

[a] The system organ class term and preferred term are coded using MedDRA version 25.1. and listed in descending order of frequency by total column. A participant is counted only once for multiple operations/procedures within preferred term/system organ class.

[b] Concomitant operations/procedures are defined as operations/procedures that were started from first study treatment intake to the last study treatment + 30 days.

A14. CS Section B.2.3.1 states that patients in FREEDOM-2 could remain on fedratinib until disease progression or unacceptable toxicity.

a) Please provide the definition of disease progression leading to treatment discontinuation, if such a definition was used.

b) Please state whether the same criteria for discontinuation based on progression or toxicity applied to patients in the BAT arm.

Response:

a) Disease progression leading to treatment discontinuation was defined in the CSR as participants being allowed to continue study treatment until occurrence of unacceptable toxicity, lack of therapeutic effect, progression of disease according to the IWG-MRT 2013 criteria or withdrawal of consent.

b) Correct. The criteria for discontinuation based on progression or toxicity applied to patients in BAT because BAT was regarded as study treatment and not as concomitant treatment.

A15. CS Section B.2.5 is entitled ‘critical appraisal’ but no formal critical appraisal is provided. Please provide a critical appraisal of FREEDOM-2 using an accepted checklist for RCTs.

Response: The results from FREEDOM-2 have not been published in a full text journal article. Therefore, it is not appropriate to complete a critical appraisal of this study. Due to resourcing, the company will not be publishing within the next 12 months and will not carry out a critical appraisal of this study.

A16. CS Section B.2.3.1 states that patients in FREEDOM-2 were either refractory or relapsed following ruxolitinib or had specific complications or adverse events (AEs).

a) CS Table 7 states that some patients had a partial response to ruxolitinib or discontinued ruxolitinib due to physician decisions or protocol requirements.

Please explain whether these patients met the criteria for being relapsed, refractory or intolerant to ruxolitinib.

b) CS Table 7 provides data for N=190 of 201 patients. Please provide data for the remaining 11 patients.

c) Of the patients i) receiving and ii) not receiving ruxolitinib in the BAT arm, please state how many entered the trial based on AEs/intolerance to ruxolitinib and how many due to being relapsed/refractory following ruxolitinib.

Response:

a) Correct. Participants who had previously been exposed to ruxolitinib, and met at least 1 of the following criteria (a and/or b):

    a. Treatment with ruxolitinib for ≥ 3 months with inadequate efficacy response (refractory) defined as < 10% spleen volume reduction by MRI or < 30% decrease from baseline in spleen size by palpation or regrowth (relapsed) to these parameters following an initial response.

    b. Treatment with ruxolitinib for ≥ 28 days complicated by any of the following (intolerant): Development of a red blood cell transfusion requirement (at least 2 units/month for 2 months) or grade ≥ 3 AEs of thrombocytopenia, anaemia, hematoma, and/or haemorrhage whilst on treatment with ruxolitinib.

    Therefore, patients who had a partial response to ruxolitinib or discontinued ruxolitinib due to physician decisions or protocol requirements in CS Table 7 were considered relapsed, refractory, or intolerant to ruxolitinib.

b) Data for the remaining 11 patients are presented in Table 3.

Table 3. FREEDOM-2: additional reasons for ruxolitinib discontinuation by investigator assessment (ITT population)

	Fedratinib (N = 134)	BAT (N = 67)	Total (N = 201)
Clinical trial end	0	1 (1.5)	1 (0.5)
Course complete	5 (3.7)	3 (4.5)	8 (4.0)
Missing	2 (1.5)	0	2 (1.0)

BAT = best available therapy; ITT = intention to treat.

c)

i. 52 patients received ruxolitinib in the BAT arm of FREEDOM-2, 9 of which entered the trial based on AEs/intolerance to ruxolitinib and 43 due to being relapsed/refractory following ruxolitinib.

ii. 15 patients did not receive ruxolitinib in the BAT arm and 3 of which entered the trial based on AEs/intolerance to ruxolitinib and 12 due to being relapsed/refractory following prior ruxolitinib.

A17. CS Table 8 outlines the FREEDOM-2 analysis populations.

a) Please provide the reasons why 20% were not eligible for the per protocol population (N and %, per arm).

b) Please provide the reasons why 23% did not receive a health-related quality-of-life (HRQoL) assessment, i.e., baseline + at least one further assessment (N and %, per arm).

Response:

a) The per-protocol population consists of all randomised patients who receive the treatment they are assigned to by randomisation, has no important violation of inclusion/exclusion criteria and no other important protocol deviations that could impact on efficacy outcome. The important protocol deviations that will exclude subjects from the per protocol population were defined as follows:

i. Did not meet one of the following inclusion criteria:

1. Inclusion 3: diagnosis of primary myelofibrosis (PMF), or diagnosis of post-ET or post-PV myelofibrosis

2. Inclusion 4: has DIPSS Risk score of Intermediate-2 or High

3. Inclusion 5: has a measurable splenomegaly (spleen volume of ≥ 450 cm3 by MRI or CT-scan and by palpable spleen measuring ≥ 5 cm below the left costal margin)

4. Inclusion 6: has a measurable total symptoms score (≥ 1) per MFSAF

5. Inclusion 7: meets ruxolitinib failure definition

ii. Meets one of the following exclusion criteria but randomised

1. Exclusion 10: received ruxolitinib within 14 days prior to randomisation

2. Exclusion 11: previous exposure to Janus kinase (JAK) inhibitor(s) other than ruxolitinib treatment

3. Missing baseline spleen volume assessment

4. Missing EOC 6 spleen volume assessment (except for PD or death prior to EOC6 assessment)

Subjects with additional important protocol deviations that have potential impact on efficacy outcome based on clinical review in a blinded manner could also be excluded from the per protocol population. The study excluded those patients who met at least one of the following criteria: (1) Violated selected inclusion criteria or met selected exclusion criteria; (2) no baseline spleen volume, (3) no EOC6 spleen volume (exclude early progressive disease/death) and (4) important protocol deviations that the clinical team believed have potential impact on efficacy. Derivation of the per-protocol population was based on a complex procedure involving multiple steps and criteria by data and clinical review; therefore, we currently do not have the breakdown of reasons for exclusion in this population.

b) The HRQoL population consists of all randomly assigned participants who had an evaluable assessment of a given PRO/HRQoL measure at baseline

and at least 1 evaluable assessment of a given PRO/HRQoL measure postbaseline. Derivation of the HRQoL population was based on a complex procedure involving multiple steps and criteria by data and clinical review; therefore, we currently do not have the breakdown of reasons for exclusion in this population.

A18. Regarding patient disposition and treatment discontinuations in FREEDOM-2 (CS Appendix D.2, Table 22), please confirm whether data listed under 'BAT' include those listed under 'Fedratinib (crossover)'. So for example, if there were 6 discontinuations due to death in the BAT arm, and 5 in the fedratinib crossover group, then can we assume there was 1 such event whilst on BAT treatment (without crossover)?

Response: Correct. The 6 discontinuations due to death in the BAT arm, includes the 5 in the fedratinib crossover group; therefore, the other 1 event occurred whilst on BAT treatment (without crossover).

Clinical effectiveness: Outcomes and censoring

A19. PRIORITY For the following outcomes, please clarify whether data were censored at crossover for patients in the BAT arm who crossed over to fedratinib:

a) Spleen and symptom response rates (CS Tables 13 to 18)

b) Durability of spleen or symptom response (CS Figures 6, 7, 8).

c) Spleen and disease progression-free survival (SDPFS) (CS Figure 9)

d) Overall survival (CS Figure 10)

e) EORTC QLQ-C30 (CS Figures 11 to 25) and EQ-5D-5L (CS Figures 26 to 27)

f) Treatment exposure (CS Table 26)

g) Adverse events (CS Section B.2.10.2)

Response:

a) Not censored

b) Not censored

c) Not censored

d) Not censored

e) Not censored

f) Not censored

g) Not censored

A20. CS Section B.2.12 states that a ≥ 50% reduction in Myelofibrosis Symptom Assessment from total symptom score (MFSAF TSS) is a clinically meaningful threshold for symptom response. Please comment on the test-retest characteristics of the MFSAF TSS, whether this measure is subject to fluctuation over time and whether this has any impact on the appropriateness of using such a measure to define the duration of response.

Response: To focus on producing responses to questions identified as priority by the External Assessment Group (EAG), we have not provided a response to this question.

A21. The IWG-MRT 2013 revised response criteria for myelofibrosis (Tefferi *et al*., 2013, CS ref 52) state that the primary contributors of decreased health-related quality of life in myelofibrosis are anaemia, splenomegaly and constitutional symptoms, and go on to provide criteria for anaemia response, spleen response (spleen volume reduction [SVR] ≥ 35%) and symptoms response.

a) Please justify why anaemia response is not given the same priority in the company submission as spleen and symptom response and is not used in the model.

b) For anaemia response data (CS page 58): Please state whether these data relate to the end of cycle six (EOC6), provide the denominators, and state

how patients with missing assessment at EOC6 or who progressed before EOC6 were analysed.

c) Please state how many anaemia responses were due to a ≥ 2 g/dL increase in haemoglobin level, and how many due to transfusion-dependent participants becoming transfusion independent (N and % per arm).

d) Please comment on the finding that anaemia response was slightly worse in the fedratinib group than the BAT group (CS page 58).

e) CS Table 2 (the Decision Problem) states that outcomes in the NICE scope and company submission included *"haematological parameters (including red blood cell transfusion and blood count)".* Other than anaemia response, these outcomes are not reported. Please provide these if available.

Response:

a) Spleen response is the primary outcome for the FREEDOM-2 trial. In FREEDOM-2, anaemia response was reported in only 19.8% of participants in the fedratinib arm and 22.6% of participants in the BAT arm. Spleen response is a more appropriate measure as there are other symptoms patients experienced in FREEDOM-2.

b) Anaemia response was analysed from baseline to the end of treatment and at any time during treatment based on the ITT population. The ITT population with evaluable anaemia response included 101 participants in the fedratinib arm and 53 in the BAT arm.

c) A summary of transfusion dependency at baseline, during treatment, and postbaseline is presented in Table 4.

Table 4. FREEDOM-2: Summary of RBC transfusion dependency at baseline, during treatment and postbaseline (ITT population)

	Fedratinib (N = 134)	BAT (N = 67)	Total (N = 201)
RBC Transfusion Rate (unit per patient per 28 days), n	96	42	138
Mean (SD)	1.935 (2.0898)	1.408 (1.2085)	1.775 (1.8775)
Baseline transfusion dependence status[a], n (%)			
Yes	29 (21.6)	11 (16.4)	40 (19.9)
No	105 (78.4)	56 (83.6)	161 (80.1)
Postbaseline transfusion independence status of those who were transfusion dependent at baseline[b], n (%)			
Yes	1 (0.7)	2 (3)	3 (1.5)
No	28 (20.9)	9 (13.4)	37 (18.4)
Postbaseline transfusion independence status of those who were NOT transfusion dependent at baseline[c], n (%)			
Yes	25 (18.7)	19 (28.4)	44 (21.9)
No	80 (59.7)	37 (55.2)	117 (58.2)

Note: Transfusion rate = units of transfusions that occurred from first dose of study medication to last dose of study medication + 30 days/on-treatment period (days) * 28 days. For fedratinib arm, only participants initially randomly assigned to this arm are included.

For BAT participants who crossed over, only data before crossover are included. For transfusion-independent patients at baseline, a responder is defined as a ≥ 20 g/L increase in haemoglobin level; for transfusion-dependent patients at baseline, a responder is defined as becoming transfusion-independent postbaseline.

[a] Transfusion dependence at baseline is defined as receiving ≥ 6 units of packed red blood cells, in the 12 weeks prior to study randomisation, for a haemoglobin level of < 85 g/L, in the absence of bleeding or treatment-induced anaemia. In addition, the most recent transfusion episode must have occurred in the 28 days prior to randomisation.

[b] Transfusion independence postbaseline is defined as absence of on-treatment RBC transfusion during any consecutive 'rolling' 12-week interval during the treatment phase, capped by a haemoglobin level of ≥ 85 g/L.

[c] Transfusion dependence at postbaseline is defined as receiving ≥ 6 units of packed red blood cells, in any consecutive 'rolling' 12-weeks interval during the treatment phase.

d) Due to 2:1 randomisation, there is a difference in the number of patients in the fedratinib arm and the BAT arm; however, anaemia response was reported in only 19.8% of participants in the fedratinib arm and 22.6% in the BAT arm. Therefore, there is not a considerable difference, and the fedratinib group does not show as slightly worse compared with the BAT group.

e) RBC transfusion is reported above in A21-c (Table 4). Platelet transfusion rate was recorded and presented in Table 5.

Table 5. FREEDOM-2: Summary of platelet transfusion during treatment (ITT population)

	Fedratinib (N = 134)	BAT (N = 67)	Total (N = 201)
Platelets transfusion rate (unit per patient per 28 days), n	20	7	27
Mean (SD)	0.487 (0.7253)	2.843 (5.7614)	1.098 (3.0251)

Note: Transfusion rate = units of transfusions that occurred from first dose of study medication to last dose of study medication + 30 days/on-treatment period (days) * 28 days. For fedratinib arm, only participants initially randomly assigned to this arm are included. For BAT participants who crossed over, only data before crossover are included.

A22. CS Table 5 states that in FREEDOM-2, the durability of spleen volume response (≥ 35% SVR) was assessed via magnetic resonance imaging (MRI)/ computed tomography (CT). Please state how frequently patients were assessed via MRI/CT, both during the first 6 cycles and subsequently. If this was infrequent, then please explain how the regular events in CS Figure 6 were determined.

Response: Patients were assessed by MRI/CT for durability of spleen volume response during screening at the end of cycle 3, 6, 12, 18, 24, every sixth cycle after cycle 24, and at the end of treatment visit.

A23. For spleen and disease progression-free survival (SDPFS) in FREEDOM-2 (CS Figure 9), please provide the definition of disease progression used to determine SDPFS (i.e., all event types included under 'progression') and how this relates to the modified IWG-MRT 2013 criteria. Please also provide a reference to the modified criteria.

Response: The International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) criteria were modified in 2013 to provide a standardised approach for assessing disease progression in myelofibrosis.

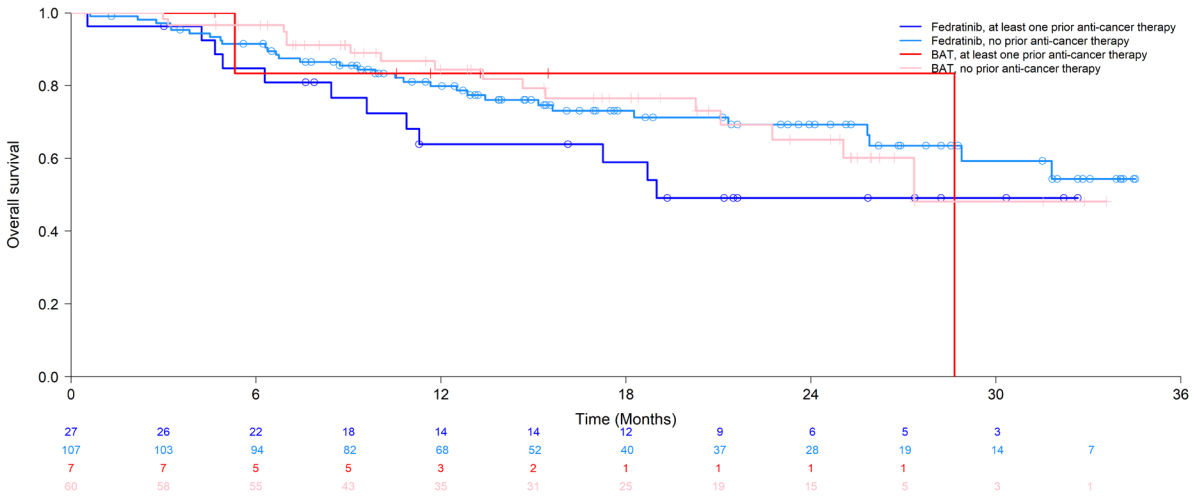
- The modified criteria consider both clinical and haematological parameters to define disease progression.
- Key components include changes in spleen size, symptoms, and overall survival.

The modified criteria are used to evaluate treatment response and progression in clinical trials, including the FREEDOM-2 trial.

A24. CS Table 19 EORTC QLQ-C30 results at baseline. CS states (p40) "*there was an imbalance in mean EORTC QLQ-C30 scores for most domains, demonstrating slightly better health status for participants in the fedratinib group than in the BAT group in all domains except for diarrhoea and appetite loss*." Later, when considering the baseline characteristics the CS states (p63) " *a higher proportion of participants in the fedratinib arm received at least 1 prior systemic anticancer therapy (20.1%) compared with participants in the BAT arm (10.4%). Participants who received more than 4 prior anticancer therapies (5.2% in fedratinib, 0 in BAT) are presumably sicker compared with participants with less than 4 prior anticancer therapies. As such, OS estimates would favour the healthier population in the BAT arm*" Please comment on the inconsistency. Does the company believe there are genuine imbalances in health status between the arms, and if so, in which direction?

Response: Further assessment of the stratified Kaplan-Meier curves showed an imbalance of prognostic factors. More patients in the fedratinib arm received at least 1 prior systemic anticancer therapy (20.1%) compared with patients in the BAT arm (10.4%). Further, some participants received more than 4 prior anticancer therapies (5.2% in fedratinib, 0 in BAT). Patients receiving more rounds of therapy are presumably sicker compared with participants with less prior anticancer therapies. As such, OS estimates would favour the healthier population in the BAT arm. Figure 1 presents the OS Kaplan-Meier curves by systemic anticancer therapy in fedratinib and BAT arms. Fedratinib and BAT patients with no prior anticancer therapy (light blue and pink, respectively) have similar survival. The patients with at least 1 systemic anticancer therapy in the fedratinib arm (dark blue) have worse survival compared with patients with no prior anticancer therapy (light blue).

Figure 1. FREEDOM-2: Kaplan-Meier overlay of overall survival for ITT populations (fedratinib and BAT arms), stratified by systemic anticancer therapy



A25. Regarding SACT data for treatment duration:

a) Please clarify whether treatment duration in SACT (CS Figure 33) is equivalent to time to discontinuation (TTD) in FREEDOM-2 (CS Figure 38).

b) Please comment on possible reasons why TTD for fedratinib appears shorter in SACT (CS Figure 33) than in FREEDOM-2 (CS Figure 38).

Response:

a) Correct. Treatment duration in SACT was equivalent to time to discontinuation.

b) The SACT is a real-world data set that is likely variable; there is possibility of diverse characteristics, comorbidities, and treatment histories having an influence on TTD. In addition, the SACT data set is a small cohort of patients: 54 patients received treatment with fedratinib.

A26. Regarding SACT data for overall survival (OS):

a) Please explain why the OS data with February 2024 cut-off (CS Figure 34) does not appear in the SACT report (CS reference 46).

b) Please provide a 95% CI for the median overall survival in SACT (15.4 months).

c) Please comment on possible reasons why overall survival for fedratinib appears shorter in SACT (median OS 15.4 months, CS Figure 34) than in FREEDOM-2 (median OS not estimable, 95% CI: 26 months to not estimable; CS Figure 10).

Response:

a) SACT OS data are attached.

b) For SACT median OS of 15.4 months, confidence intervals could not be produced as there was an insufficient number of events at the time the report was produced.

c) SACT data collected during the CDF period provide an opportunity for potential validation of the data from FREEDOM-2. SACT data for fedratinib display a more pessimistic OS outcome when compared with FREEDOM-2. However, 1-to-1 comparison is challenging due to some key differences:

   - FREEDOM-2 and SACT differ in terms of study population. The SACT cohort includes older patients, with a median age of 72 years (48% of patients aged 70-79 years and 11% > 80 years). The FREEDOM-2 population was younger, with a median age of 70 years. SACT data display a larger proportion of male versus female patients (76% vs. 56%). Additionally, PS was missing for 48% of the SACT data set, making it difficult to compare the disease burden between FREEDOM-2 and the SACT data set.
   - Real-world evidence carries higher uncertainty and thus has lower confidence than evidence gathered in a clinical trial setting.

- Median treatment duration in SACT is shorter than median treatment duration in FREEDOM-2. The all-treated fedratinib median treatment duration is 52.5 weeks, whereas in SACT, it is 24.4 weeks. This difference will likely be the source of further uncertainty when comparing OS outcomes between the SACT data set and FREEDOM-2.

A27. PRIORITY In relation to the AE data for FREEDOM-2:

a) What does 'all-treated' population refer to in CS Table 26? Is this equivalent to the 'Safety population' defined in CS Table 8?

b) In the presentation of AEs for 'all-treated' patients, are the events reported for 'BAT all-treated' restricted to the time up to crossover for patients who crossed over to fedratinib?

c) For AEs leading to death (CS Section B.2.10.6), please confirm whether any of were considered treatment-related. Please provide a table of treatment-related AEs leading to death.

d) In the AE tables (CS Table 28 onwards), please clarify why several of the treatment-related AEs are marked as NR. Was there a frequency cut-off in reporting AEs?

e) For serious AEs (SAEs, CS Table 30+31), please report these data regardless of frequency cut-off, if available.

f) Please provide a table of grade 3/4 AEs (all and treatment-related).

g) Please provide a separate table of AE data for the adverse events listed under 'special warnings and precautions' in the summary of product characteristics (SmPC). These include: encephalopathy; Wernicke's encephalopathy; anaemia; thrombocytopenia; neutropenia; nausea; vomiting; diarrhoea; hepatic toxicity (elevations of alanine aminotransferase [ALT] and aspartate aminotransferase [AST]); elevated amylase/lipase; elevated creatinine; major adverse cardiac events (MACE); thrombosis; and secondary malignancies.

Response:

a) Correct. The ‘all-treated’ population is equivalent to the ‘safety’ population defined in CS Table 8.

b) For crossover participants in the BAT arm, only data before crossover are included.

c) AEs leading to death were reported as treatment-emergent; AEs leading to death that were treatment-related were not considered as an analysis.

d) All AEs were recorded by the Investigator from the time the participant signs informed consent until 30 days after the last dose of fedratinib or comparator as well as those that were suspected of being related to fedratinib or comparator. For each AE, the Investigator provided information on the relationship to fedratinib or comparator. Suspected relationship was defined as there was a reasonable possibility that the administration of fedratinib or BAT caused the AE. ‘Reasonable possibility’ meant that there was evidence to suggest a causal relationship between fedratinib or BAT and the AE. Not suspected relationship was defined as a causal relationship of the AE to fedratinib or BAT administration was unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provided a sufficient explanation for the AE. Therefore, there are several treatment-related AEs marked as NR in the tables because the AEs were not reported as suspected to be treatment-related by the Investigator.

e) There was no frequency cutoff. The several treatment-related AEs marked as NR in the tables are due to the AEs not being reported as suspected to be treatment-related by the Investigator.

f) Grade 3/4 AEs for all-treated populations and crossover population for treatment-emergent and treatment-related are reported inTable 6 Table 6 and Table 7.

Table 6. FREEDOM-2: CTCAE Grade 3/4 treatment-emergent and treatment-related TEAEs (all-treated population)

	Treatment-emergent		Treatment-related	
System organ class, preferred term, n (%)	Fedratinib (n = 134)	BAT (n = 67)	Fedratinib (n = 134)	BAT (n = 67)
Participants with ≥ 1 CTCAE Grade 3/4 TEAE	103 (76.9)	37 (55.2)	62 (46.3)	10 (14.9)
Blood and lymphatic system disorder	67 (50)	21 (31.3)	34 (25.4)	9 (13.4)
Anaemia	43 (32.1)	14 (20.9)	13 (9.7)	6 (9)
Thrombocytopenia	36 (26.9)	5 (7.5)	23 (17.2)	3 (4.5)
Leukocytosis	4 (3)	4 (6)	NR	NR
Neutropenia	4 (3)	1 (1.5)	3 (2.2)	1 (1.5)
Leukopenia	2 (1.5)	1 (1.5)	2 (2.5)	1 (1.5)
Lymphopenia	1 (0.7)	1 (1.5)	1 (0.7)	1 (1.5)
Splenic infarction	0	1 (1.5)	NR	NR
Spontaneous haematoma	0	1 (1.5)	NR	NR
Metabolism and nutrition disorders	22 (16.4)	4 (6)	8 (6)	0
Hyperkalaemia	11 (8.2)	0	4 (3)	0
Decreased appetite	4 (3)	1 (1.5)	2 (1.5)	0
Hypokalaemia	3 (2.2)	1 (1.5)	1 (0.7)	0
Hyponatraemia	2 (1.5)	0	1 (0.7)	0
Gout	1 (0.7)	0	NR	NR
Haemosiderosis	1 (0.7)	0	NR	NR
Hypertriglyceridaemia	1 (0.7)	0	NR	NR
Hyperuricaemia	1 (0.7)	1 (1.5)	NR	NR
Vitamin B1 deficiency	1 (0.7)	0	1 (0.7)	0
Tumour lysis syndrome	0	1 (1.5)	NR	NR
Infections and infestations	19 (14.2)	9 (13.4)	1 (0.7)	2 (3)
Pneumonia	3 (2.2)	3 (4.5)	0	1 (1.5)
COVID-19	2 (1.5)	3 (4.5)	NR	NR
Escherichia sepsis	2 (1.5)	0	1 (0.7)	0
Septic shock	2 (1.5)	0	NR	NR
Urinary tract infection	2 (1.5)	0	NR	NR
COVID-19 pneumonia	1 (0.7)	1 (1.5)	NR	NR
Capnocytophaga infection	1 (0.7)	0	NR	NR
Cellulitis	1 (0.7)	0	NR	NR
Epididymitis	1 (0.7)	0	NR	NR
Lower respiratory tract infection	1 (0.7)	0	NR	NR
Neutropenic sepsis	1 (0.7)	0	NR	NR
Pneumonia bacterial	1 (0.7)	0	NR	NR
Pyelonephritis chronic	1 (0.7)	0	NR	NR
Respiratory tract infection	1 (0.7)	1 (1.5)	NR	NR
Soft tissue infection	1 (0.7)	0	NR	NR
Streptococcal bacteraemia	1 (0.7)	0	NR	NR
Tooth abscess	1 (0.7)	0	NR	NR

System organ class, preferred term, n (%)	Treatment-emergent		Treatment-related	
	Fedratinib (n = 134)	BAT (n = 67)	Fedratinib (n = 134)	BAT (n = 67)
Tooth infection	1 (0.7)	0	NR	NR
Bronchitis	0	1 (1.5)	NR	NR
Cholecystitis infective	0	1 (1.5)	NR	NR
Lymph node tuberculosis	0	1 (1.5)	0	1 (1.5)
Peritonitis	0	1 (1.5)	NR	NR
Suspected COVID-19	0	1 (1.5)	NR	NR
Renal and urinary disorders	19 (14.2)	3 (4.5)	13 (9.7)	0
Acute kidney injury	9 (6.7)	1 (1.5)	3 (2.2)	0
Chronic kidney disease	5 (3.7)	0	5 (3.7)	0
Renal failure	4 (3)	0	3 (2.2)	0
Renal impairment	3 (2.2)	0	3 (2.2)	0
Calculus urinary	0	1 (1.5)	NR	NR
Renal colic	0	1 (1.5)	NR	NR
Gastrointestinal disorders	16 (11.9)	1 (1.5)	6 (4.5)	0
Ascites	3 (2.2)	0	NR	NR
Abdominal pain	2 (1.5)	0	1 (0.7)	0
Abdominal pain upper	2 (1.5)	1 (1.5)	1 (0.7)	0
Diarrhoea	2 (1.5)	0	1 (0.7)	0
Gastrointestinal haemorrhage	2 (1.5)	0	NR	NR
Nausea	2 (1.5)	0	2 (1.5)	0
Abdominal discomfort	1 (0.7)	0	NR	NR
Constipation	1 (0.7)	0	NR	NR
Gastric ulcer	1 (0.7)	0	NR	NR
Intestinal obstruction	1 (0.7)	0	NR	NR
Subileus	1 (0.7)	0	1 (0.7)	0
Upper gastrointestinal haemorrhage	1 (0.7)	0	1 (0.7)	0
Varices oesophageal	1 (0.7)	0	NR	NR
General disorders and administration site conditions	16 (11.9)	4 (6)	5 (3.7)	0
General physical health deterioration	11 (8.2)	1 (1.5)	2 (1.5)	0
Asthenia	4 (3)	1 (1.5)	2 (1.5)	0
Fatigue	2 (1.5)	2 (3)	NR	NR
Generalised oedema	1 (0.7)	1 (1.5)	1 (0.7)	0
Pyrexia	0	2 (3)	NR	NR
Investigations	15 (11.2)	0	9 (6.7)	0
Alanine aminotransferase increased	6 (4.5)	0	5 (3.7)	0
Glomerular filtration rate decreased	3 (2.2)	0	2 (1.5)	0
Aspartate aminotransferase increased	2 (1.5)	0	1 (0.7)	0
Gamma-glutamyltransferase increased	2 (1.5)	0	1 (0.7)	0
Blood creatinine increased	1 (0.7)	0	1 (0.7)	0
Creatinine renal clearance decreased	1 (0.7)	0	1 (0.7)	0
Ejection fraction decreased	1 (0.7)		NR	NR

System organ class, preferred term, n (%)	Treatment-emergent		Treatment-related	
	Fedratinib (n = 134)	BAT (n = 67)	Fedratinib (n = 134)	BAT (n = 67)
Glomerular filtration rate increased	1 (0.7)	0	NR	NR
Haemoglobin decreased	1 (0.7)	0	NR	NR
Liver function test abnormal	1 (0.7)	0	NR	NR
Blood bilirubin increased	0	1 (1.5)	NR	NR
C-reactive protein increased	0	1 (1.5)	NR	NR
Cardiac disorders	11 (8.2)	1 (1.5)	2 (1.5)	0
Cardiac failure	4 (3)	1 (1.5)	NR	NR
Cardiac failure congestive	3 (2.2)	0	NR	NR
Atrial fibrillation	2 (1.5)	0	2 (1.5)	0
Stress cardiomyopathy	1 (0.7)	0	NR	NR
Tricuspid valve incompetence	1 (0.7)	0	NR	NR
Ventricular tachycardia	1 (0.7)	0	NR	NR
Respiratory, thoracic and mediastinal disorders	6 (4.5)	5 (7.5)	1 (0.7)	0
Dyspnoea	3 (2.2)	0	1 (0.7)	0
Emphysema	2 (1.5)	0	NR	NR
Epistaxis	1 (0.7)	0	NR	NR
Organising pneumonia	1 (0.7)	0	NR	NR
Pulmonary oedema	1 (0.7)	0	NR	NR
Lung infiltration	0	1 (1.5)	NR	NR
Pulmonary embolism	0	1 (1.5)	NR	NR
Pulmonary hypertension	0	1 (1.5)	NR	NR
Respiratory distress	0	1 (1.5)	NR	NR
Respiratory failure	0	1 (1.5)	NR	NR
Eye disorders	5 (3.7)	0	3 (2.2)	0
Uveitis	2 (1.5)	0	2 (1.5)	0
Iridocyclitis	1 (0.7)	0	1 (0.7)	0
Retinal oedema	1 (0.7)	0	NR	NR
Vitreous haemorrhage	1 (0.7)	0	NR	NR
Neoplasms benign, malignant and unspecified (including cysts and polyps)	5 (3.7)	0	NR	NR
Adenocarcinoma gastric	1 (0.7)	0	NR	NR
Adenocarcinoma of colon	1 (0.7)	0	NR	NR
Penile cancer	1 (0.7)	0	NR	NR
Squamous cell carcinoma	1 (0.7)	0	NR	NR
Squamous cell carcinoma of skin	1 (0.7)	0	NR	NR
Transformation to acute myeloid leukaemia	1 (0.7)	0	NR	NR
Injury, poisoning and procedural complications	4 (3)	0	NR	NR
Fall	1 (0.7)	0	NR	NR
Patella fracture	1 (0.7)	0	NR	NR

System organ class, preferred term, n (%)	Treatment-emergent		Treatment-related	
	Fedratinib (n = 134)	BAT (n = 67)	Fedratinib (n = 134)	BAT (n = 67)
Postprocedural haemorrhage	1 (0.7)	0	NR	NR
Traumatic haematoma	1 (0.7)	0	NR	NR
Vascular pseudoaneurysm	1 (0.7)	0	NR	NR
Nervous system disorders	4 (3)	1 (1.5)	1 (0.7)	0
Peripheral sensory neuropathy	2 (1.5)	0	1 (0.7)	0
Headache	1 (0.7)	0	NR	NR
Metabolic encephalopathy	1 (0.7)	0	NR	NR
Sciatica	0	1 (1.5)	NR	NR
Hepatobiliary disorders	3 (2.2)	0	NR	NR
Cholecystitis acute	1 (0.7)	0	NR	NR
Hepatosplenomegaly	1 (0.7)	0	NR	NR
Portal hypertension	1 (0.7)	0	NR	NR
Skin and subcutaneous tissue disorders	3 (2.2)	4 (6)	NR	NR
Pruritus	2 (1.5)	1 (1.5)	NR	NR
Night sweats	1 (0.7)	3 (4.5)	NR	NR
Hyperhidrosis	0	1 (1.5)	NR	NR
Vascular disorders	3 (2.2)	3 (4.5)	NR	NR
Aortic aneurysm	1 (0.7)	0	NR	NR
Hypertension	1 (0.7)	1 (1.5)	NR	NR
Pallor	1 (0.7)	0	NR	NR
Aortic dissection	0	1 (1.5)	NR	NR
Haematoma	0	1 (1.5)	NR	NR
Psychiatric disorders	2 (1.5)	0	1 (0.7)	0
Delirium febrile	1 (0.7)	0	NR	NR
Mental disorder	1 (0.7)	0	1 (0.7)	0
Endocrine disorders	1 (0.7)	1 (1.5)	NR	NR
Adrenal insufficiency	1 (0.7)	0	NR	NR
Adrenal haemorrhage	0	1 (1.5)	NR	NR
Musculoskeletal and connective tissue disorders	1 (0.7)	1 (1.5)	NR	NR
Bursitis	1 (0.7)	0	NR	NR
Arthralgia	0	1 (1.5)	NR	NR
Social circumstances	1 (0.7)	0	NR	NR
Physical disability	1 (0.7)	0	NR	NR

Table 7. FREEDOM-2: CTCAE Grade 3/4 treatment-emergent and treatment-related TEAEs (crossover population)

	Treatment-emergent	Treatment-related
System organ class, preferred term, n (%)	**Fedratinib (n** = 46)	**Fedratinib (n** = 46)
Participants with ≥ 1 CTCAE Grade 3/4 TEAE	31 (67.4)	18 (39.1)
Blood and lymphatic system disorders	22 (47.8)	15 (32.6)
Anaemia	13 (28.3)	8 (17.4)
Thrombocytopenia	12 (26.1)	9 (19.6)
Neutropenia	3 (6.5)	NR
Leukocytosis	1 (2.2)	NR
Splenic infarction	1 (2.2)	NR
Infections and infestations	10 (21.7)	1 (2.2)
COVID-19	3 (6.5)	NR
Urinary tract infection	3 (6.5)	NR
Pneumonia	2 (4.3)	1 (2.2)
Abscess soft tissue	1 (2.2)	NR
Clostridium difficile infection	1 (2.2)	NR
Perineal abscess	1 (2.2)	NR
Postoperative wound infection	1 (2.2)	NR
Renal and urinary disorders	5 (10.9)	3 (6.5)
Chronic kidney disease	2 (4.3)	1 (2.2)
Haematuria	1 (2.2)	NR
Renal failure	1 (2.2)	1 (2.2)
Renal impairment	1 (2.2)	1 (2.2)
General disorders and administration site conditions	4 (8.7)	1 (2.2)
Asthenia	3 (6.5)	1 (2.2)
General physical health deterioration	1 (2.2)	NR
Gastrointestinal disorders	3 (6.5)	1 (2.2)
Abdominal pain	1 (2.2)	NR
Diarrhoea	1 (2.2)	1 (2.2)
Duodenal ulcer haemorrhage	1 (2.2)	NR
Metabolism and nutrition disorders	2 (4.3)	1 (2.2)
Hyperkalaemia	1 (2.2)	NR
Hypocalcaemia	1 (2.2)	1 (2.2)
Tumour lysis syndrome	1 (2.2)	1 (2.2)
Vascular disorders	2 (4.3)	NR
Haematoma	1 (2.2)	NR
Hypertension	1 (2.2)	NR
Cardiac disorders	1 (2.2)	NR
Coronary artery stenosis	1 (2.2)	NR
Injury, poisoning and procedural complications	1 (2.2)	NR
Contusion	1 (2.2)	NR

System organ class, preferred term, n (%)	Treatment-emergent Fedratinib (n = 46)	Treatment-related Fedratinib (n = 46)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (2.2)	NR
Transformation to acute myeloid leukaemia	1 (2.2)	NR
Nervous system disorders	1 (2.2)	NR
Headache	1 (2.2)	NR
Respiratory, thoracic and mediastinal disorders	1 (2.2)	1 (2.2)
Dyspnoea	1 (2.2)	1 (2.2)
Skin and subcutaneous tissue disorders	1 (2.2)	NR
Pruritus	1 (2.2)	NR

g) AE data reported to be of special interest are reported in Table 8 and Table 9 for all-treated populations and the crossover population, respectively, and include treatment-emergent and treatment-related AEs.

Table 8. FREEDOM-2: AEs of special interest (AESI) treatment-emergent and treatment-related TEAEs (all-treated population)

System organ class, preferred term, n (%)	Treatment-emergent Fedratinib (n = 134)	Treatment-emergent BAT (n = 67)	Treatment-related Fedratinib (n = 134)	Treatment-related BAT (n = 67)
Subjects with at least 1 AESI	107 (79.9)	29 (43.3)	57 (42.5)	9 (13.4)
Grade 3 or 4 Anaemia	44 (32.8)	14 (20.9)	13 (9.7)	6 (9)
Anaemia	43 (32.1)	14 (20.9)	13 (9.7)	6 (9)
Haemoglobin decreased	1 (0.7)	0	NR	NR
Cardiac Failure/Cardiomyopathy	38 (28.4)	8 (11.9)	3 (2.2)	1 (1.5)
Oedema peripheral	26 (19.4)	7 (10.4)	2 (1.5)	1 (1.5)
Cardiac failure	6 (4.5)	1 (1.5)	NR	NR
Ascites	5 (3.7)	1 (1.5)	1 (0.7)	0
Cardiac failure congestive	3 (2.2)	0	NR	NR
Peripheral swelling	3 (2.2)	1 (1.5)	NR	NR
Ejection fraction decreased	2 (1.5)	0	NR	NR
Cardiomyopathy	1 (0.7)	0	NR	NR
Hypervolaemia	1 (0.7)	0	NR	NR
Pulmonary congestion	1 (0.7)	0	NR	NR
Pulmonary oedema	1 (0.7)	0	NR	NR
Right ventricular dysfunction	1 (0.7)	0	NR	NR
Right ventricular failure	1 (0.7)	0	NR	NR
Stress cardiomyopathy	1 (0.7)	0	NR	NR
Grade 3 or 4 Thrombocytopenia	36 (26.9)	5 (7.5)	23 (17.2)	3 (4.5)
Thrombocytopenia	36 (26.9)	5 (7.5)	23 (17.2)	3 (4.5)
Encephalopathy, Including Wernicke's	5 (3.7)	3 (4.5)	15 (11.2)	0

System organ class, preferred term, n (%)	Treatment-emergent		Treatment-related	
	Fedratinib (n = 134)	BAT (n = 67)	Fedratinib (n = 134)	BAT (n = 67)
Dysgeusia	5 (3.7)	0	4 (3)	0
Peripheral sensory neuropathy	3 (2.2)	1 (1.5)	3 (2.2)	0
Amnesia	3 (2.2)	0	3 (2.2)	0
Paraesthesia	2 (1.5)	0	NR	NR
Confusional state	2 (1.5)	0	NR	NR
Herpes zoster	2 (1.5)	1 (1.5)	1 (0.7)	0
Hypoaesthesia	2 (1.5)	0	2 (1.5)	0
Vision blurred	2 (1.5)	0	1 (0.7)	0
Burning sensation	1 (0.7)	0	NR	NR
Delirium febrile	1 (0.7)	0	NR	NR
Epilepsy	1 (0.7)	0	NR	NR
Memory impairment	1 (0.7)	0	NR	NR
Metabolic encephalopathy	1 (0.7)	0	NR	NR
Post-herpetic neuralgia	1 (0.7)	0	NR	NR
Taste disorder	1 (0.7)	0	NR	NR
Wernicke’s encephalopathy	1 (0.7)	0	1 (0.7)	0
Bradyphrenia	0	1 (1.5)	NR	NR
Febrile convulsion	0	1 (1.5)	NR	NR
Peripheral sensorimotor neuropathy	0	1 (1.5)	NR	NR
Thiamine levels below normal range with or without signs or symptoms of WE	27 (20.1)	3 (4.5)	18 (13.4)	0
Vitamin B1 decreased	17 (12.7)	2 (3)	11 (8.2)	0
Vitamin B1 deficiency	10 (7.5)	1 (1.5)	7 (5.2)	0
Grade 3 or 4 ALT, AST, or Total Bilirubin Elevation	12 (9)	1 (1.5)	5 (3.7)	0
Alanine aminotransferase increased	6 (4.5)	0	5 (3.7)	0
Ascites	3 (2.2)	0	NR	NR
Aspartate aminotransferase increased	2 (1.5)	0	1 (0.7)	0
Gamma-glutamyltransferase increased	2 (1.5)	0	1 (0.7)	0
Hepatosplenomegaly	1 (0.7)	0	NR	NR
Liver function test abnormal	1 (0.7)	0	NR	NR
Portal hypertension	1 (0.7)	0	NR	NR
Varices oesophageal	1 (0.7)	0	NR	NR
Blood bilirubin increased	0	1 (1.5)	NR	NR
Secondary Malignancies	10 (7.5)	3 (4.5)	1 (0.7)	1 (1.5)
Squamous cell carcinoma	4 (3)	2 (3)	0	1 (1.5)
Squamous cell carcinoma of skin	4 (3)	1 (1.5)	1 (0.7)	0
Adenocarcinoma gastric	1 (0.7)	0	NR	NR
Adenocarcinoma of colon	1 (0.7)	0	NR	NR
Basal cell carcinoma	1 (0.7)	0	NR	NR
Malignant melanoma	1 (0.7)	0	NR	NR
Penile cancer	1 (0.7)	0	NR	NR

System organ class, preferred term, n (%)	Treatment-emergent		Treatment-related	
	Fedratinib (n = 134)	BAT (n = 67)	Fedratinib (n = 134)	BAT (n = 67)
Renal neoplasm	1 (0.7)	0	NR	NR
Transformation to acute myeloid leukaemia	1 (0.7)	0	NR	NR
Adrenal neoplasm	0	1 (1.5)	NR	NR
Grade 3 or 4 Hyperamylasemia or Hyperlipasemia	7 (5.2)	2 (3)	3 (2.2)	0
Ascites	3 (2.2)	0	NR	NR
Abdominal pain	2 (1.5)	0	1 (0.7)	0
Abdominal pain upper	2 (1.5)	1 (1.5)	1 (0.7)	0
Nausea	2 (1.5)	0	2 (1.5)	0
Blood bilirubin increased	0	1 (1.5)	NR	NR
Secondary Malignancies - Progression to AML	1 (0.7)	0	NR	NR
Transformation to acute myeloid leukaemia	1 (0.7)	0	NR	NR

Table 9. FREEDOM-2: AEs of special interest treatment-emergent and treatment-related TEAEs (crossover population)

System organ class, preferred term, n (%)	Treatment-emergent	Treatment-related
	Fedratinib (n = 46)	Fedratinib (n = 46)
Participants with at least 1 AESI	28 (60.9)	19 (41.3)
Grade 3 or 4 Anaemia	13 (28.3)	8 (17.4)
Anaemia	13 (28.3)	8 (17.4)
Grade 3 or 4 Thrombocytopenia	12 (26.1)	9 (19.6)
Thrombocytopenia	12 (26.1)	9 (19.6)
Cardiac Failure/Cardiomyopathy	6 (13.0)	2 (4.3)
Oedema peripheral	6 (13.0)	2 (4.3)
Thiamine levels below normal range with or without signs or symptoms of WE	6 (13.0)	8 (8.7)
Vitamin B1 decreased	4 (8.7)	2 (4.3)
Vitamin B1 deficiency	2 (4.3)	2 (4.3)
Encephalopathy, Including Wernicke’s	3 (6.5)	1 (2.2)
Dysgeusia	1 (2.2)	1 (2.2)
Paraesthesia	1 (2.2)	NR
Secondary Malignancies	3 (6.5)	1 (2.2)
Squamous cell carcinoma of skin	2 (4.3)	1 (2.2)
Squamous cell carcinoma	1 (2.2)	NR
Transformation to acute myeloid leukaemia	1 (2.2)	NR
Grade 3 or 4 Hyperamylasemia or Hyperlipasemia	1 (2.2)	NR
Abdominal pain	1 (2.2)	NR
Secondary Malignancies - Progression to AML	1 (2.2)	NR
Transformation to acute myeloid leukaemia	1 (2.2)	NR

Section B: Clarification on cost-effectiveness data

Literature searches: Economic SLRs

B1. CS, Appendices, Sections G, H, and I. The overall search strategies for identifying studies for cost-effectiveness, health-related quality of life, and cost and resource use of the treatment have been outlined. However, search transcripts have not been reported. Please provide transcripts of the search(es) run, and clarification of the date(s) conducted.

Response: These have been provided.

B2. Please explain why your search of published cost-effectiveness studies identified HTA agency documents for ruxolitinib but none for fedratinib. For example, CADTH has produced guidance for fedratinib that reports cost per quality-adjusted life-year (QALY) (https://www.cadth.ca/sites/default/files/attachments/2021-06/CADTH_reimbursement_recommendation_fedratinib_%28inrebic%29_comp.pdf). If the reason is because the company limited its search to Feb 2020 then please provide an updated review to address this limitation.

Response: Studies published in other countries are not included as the submission focuses on NICE and studies focusing on the UK setting.

B3. Please provide an updated literature review for resource use (Appendix I) to determine whether any comparative data on resource use for fedratinib versus ruxolitinib (or versus BAT without ruxolitinib) has been published since February 2020.

Response: As for the clinical outcomes, BMS have regularly monitored and reviewed the NICE website for any updates related to drug approvals, guidelines, and evidence. Furthermore, BMS has searched for new publications, trial results, relevant recommendations, and has collaborated with key experts in the field of myelofibrosis and haematological oncology to keep up to date on any emerging evidence. No new data on resource use have been identified through this process.

Modelled comparators

B4. PRIORITY Momelotinib is now approved by NICE for the treatment of myelofibrosis-related splenomegaly or symptoms in adults with moderate to severe anaemia who have intermediate-2 or high-risk myelofibrosis, including patients who have had previous treatment with ruxolitinib (TA957). the External Assessment Group (EAG) therefore considers that there is a potential overlap between the population covered in TA957 and the population included in the company's model. Please provide an estimate of the proportion of patients within the modelled population who are likely to have moderate to severe anaemia. Please provide a cost-effectiveness comparison of fedratinib against momelotinib for this subgroup.

Response: Please see our response to question A6.

Composition of BAT

B5. PRIORITY The CS states (p94) that Table 41 shows the composition of BAT in the FREEDOM-2 trial.

a) Please provide the n/Ns that have been used to derive the percentages in the 'BAT (as comparator)' column and indicate where these data can be found in the clinical study report (CSR).

b) Please also explain why the data in the 'BAT (as comparator)' column do not correlate with those provided in Table 14.3.1.1.2.1 of the CSR which shows for example that [redacted]% had hydroxyurea and [redacted]% had RBC transfusion in the BAT arm.

c) Please update the model to use the BAT composition from FREEDOM-2 as presented in the CSR or explain why this is not appropriate.

Response:

a) The following numbers have been used in the model to derive the percentages in the 'BAT (as comparator)' column. They are retrieved from Table 14.3.1.1.2.1 in the CSR supplemental materials, using the individual BAT option category.

	Number (proportion)
Treatment	**BAT (N = 67)**
Anagrelide	0 (0%)
Busulfan	0 (0%)
Cytarabine	0 (0%)
Danazol	1 (1.5%)
Decitabine	0 (0%)
Hydroxycarbamide	1 (1.5%)
Interferon alfa	1 (1.5%)
Peginterferon alfa-2a	0 (0%)
Prednisolone	1 (1.5%)
Prednisone	1 (1.5%)
Thalidomide	1 (1.5%)
Ruxolitinib	52 (77.6%)

b) The ‘BAT (as comparator)’ column used treatments in line with the initial fedratinib in MF model. As such, the list of treatments used in BAT were kept as per the original model. Please see the response below (B5c) for an update in the model.

c) The model has been updated to include the treatment RBC, hydroxyurea, no treatment, mercaptopurine, and methylprednisolone. Including the treatments outlined in the CSR for the BAT arm leads to an increase in costs for BAT and a decrease in overall costs for fedratinib.

B6. PRIORITY The model presents the composition of BAT after fedratinib in both CS Table 41 and CS Table 65. However, the data for responders to fedratinib, labelled ‘BAT (after fedratinib, responders)’, differ between these two tables. In addition, the data used in the model for this purpose (Drug Costs cells F104:F124) appear to match the data for ‘BAT (after fedratinib, non-responders)’ (i.e., third column of CS BTable 41/second column CS Table 65).

a) Please clarify the distribution of BAT treatments assumed in the model base case for patients who initially responded to fedratinib after they move onto BAT in the model. Please also indicate how these data were derived from the

data in the CSR, and any assumptions that were made to estimate these proportions from the data available.

b) The text in the paragraph above CS Table 41 states that a scenario analysis exploring suboptimal fedratinib is conducted assuming that 32.1% of responders continue on suboptimal fedratinib after they progress on fedratinib. Please clarify if the description of suboptimal fedratinib as being 32.1% of BAT in CS Table 74 should state that this is only explored in a scenario analysis and the basecase assumes 0% suboptimal fedratinib. Please clarify whether the 'BAT (after fedratinib, responders)' column of CS Table 41 is used in this suboptimal fedratinib scenario analysis.

c) It is stated (CS, p94) that the 32.1% having suboptimal fedratinib is based on the discontinuation rate of fedratinib being 67.9% at the cutoff date in FREEDOM-2. Please justify why the proportion of patients who had not discontinued fedratinib at last follow-up is useful for informing the usage of suboptimal fedratinib in clinical practice, given that this proportion is not specific to initial responders and patients were only allowed to remain on study drug until disease progression, meaning that suboptimal fedratinib was not allowed within FREEDOM-2.

d) Please clarify if the data in the column labelled 'BAT (after fedratinib, responders)' in CS Table 65 is used in any of the scenarios presented by the company. If it is used, please clarify where the data are sourced from.

Response:

a) The distribution of BAT treatments after fedratinib for patients who initially responded to fedratinib is based on the distribution of BAT as a comparator from the CSR, Table 14.3.1.1.2.1. BAT as a comparator includes ruxolitinib, which is not given after fedratinib in BAT. This is because patients who received fedratinib have previously received ruxolitinib, and retreatment with ruxolitinib should be avoided. Therefore, the composition of BAT after fedratinib for initial responders needs to be reweighted to account for the removal of fedratinib. This is done by dividing the initial proportion of patients

receiving each treatment by the proportion of patients receiving non-JAKi treatments.

b) Suboptimal fedratinib is indeed explored only as a scenario analysis to understand the impact of reusing fedratinib after patients first discontinue fedratinib. The CS Table 41 should read as follows:

Treatment	BAT (as comparator)	BAT (after fedratinib, responders)	BAT (after fedratinib, non-responders)
Danazol	1.5%	16.7%	16.7%
Hydroxycarbamide (hydroxyurea)	1.5%	16.7%	16.7%
Interferon alfa	1.5%	16.7%	16.7%
Prednisolone	1.5%	16.7%	16.7%
Prednisone	1.5%	16.7%	16.7%
Thalidomide	1.5%	16.7%	16.7%
Ruxolitinib	77.6%	0%	0%
Fedratinib	0%	0%	0%

c) Suboptimal fedratinib refers to use of fedratinib amongst patients after loss of response or when there has not been a full response. In clinical practice use of suboptimal fedratinib is unlikely; hence, this is not modelled in the base case. Whilst it is not possible to identify rates of suboptimal fedratinib in FREEDOM-2, intuitively, patients who received suboptimal fedratinib will have not discontinued treatment. Note that the subgroup of patients who have not discontinued treatment will also include patients who are benefiting from fedratinib. Hence the use of 32.1% in a scenario represents an upper bound on actual rates of suboptimal fedratinib use in FREEDOM-2.

d) Table 65 in the CS contains a typo, where 65% of patients would wrongly receive fedratinib. This should be 0% and the proportions of patients receiving the remaining treatments should be equal to those of the column ‘BAT (after fedratinib, non-responders).’ Please see below:

Treatment	BAT (after fedratinib, responders)	BAT (after fedratinib, non-responders)
Danazol	16.7%	16.7%
Hydroxycarbamide (hydroxyurea)	16.7%	16.7%
Interferon alfa	16.7%	16.7%
Prednisolone	16.7%	16.7%
Prednisone	16.7%	16.7%
Thalidomide	16.7%	16.7%
Ruxolitinib	0%	0%
Fedratinib	0%	0%

B7. PRIORITY CS Table 41 and CS Table 65: Please clarify how the distribution of treatments for 'BAT (after fedratinib, non-responders)' has been estimated from the data in the CSR including any assumptions made. If data are available from FREEDOM-2 on the actual usage of BAT treatments after patients discontinued fedratinib, please update the model to allow these data to be used as an option.

Response: The distribution of treatments for 'BAT (after fedratinib, non-responders)' has been calculated by reweighting the BAT as comparator arm proportions and removing the patients receiving suboptimal ruxolitinib.

B8. PRIORITY The previous appraisal of fedratinib (TA756) states "*The committee understood that in practice clinicians would likely be reluctant to stop fedratinib even if the disease does not fully respond, or stops responding. This was because there would be no other treatment options. The committee concluded that it was appropriate to assume that 89% of all people starting fedratinib would continue fedratinib after their disease stops responding. This was consistent with the proportion [89%] who were assumed to continue ruxolitinib in the best available therapy arm*."

a) The text in the paragraph above CS Table 41 states that suboptimal fedratinib usage is assumed to be 0% in the base case. Please clarify why this is a reasonable assumption given the committee's previous conclusions in TA759.

b) Please provide a scenario analysis in which the proportion of patients receiving fedratinib as part of 'BAT after fedratinib' (for both responders and non-responders) matches the proportion receiving ruxolitinib in the BAT arm

(i.e., 77.6%). In this scenario, no patients should go directly to supportive care as this would reduce the proportion receiving suboptimal fedratinib via another means.

Response:

a) This is based on clinical practice and the discontinuation rate seen in the FREEDOM-2 clinical trial. As previously discussed (in response to B6), 67.9% of patients discontinued fedratinib at the end of the trial cutoff date, and data from the SACT registry reflect high discontinuation rates, which collectively demonstrate that fedratinib is unlikely to be used when there is a lack of response or loss of response. Therefore, no patients using suboptimal fedratinib are used in the model base case.

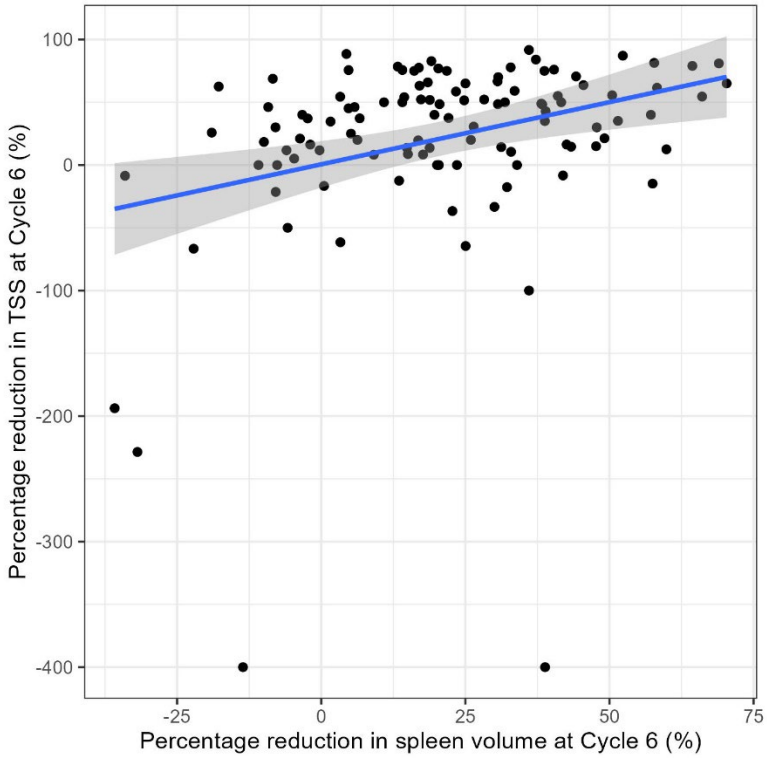
b) The scenario has been implemented in the model. This scenario incurs approximately £3,000 additional costs for fedratinib. Hence fedratinib remains dominating BAT. However, it should be noted that this scenario is highly unlikely to occur in clinical practice because most patients would move onto supportive care after failure of 2 JAKi treatments.

Definition of response within the model

B9. Response in the model is based on either spleen volume reduction or TSS response. This is described as being based on the rationale that they "*track together*" (CS, p95) suggesting that they should be highly correlated. But the figures in Tables 42 to 44 suggest that the majority of patients categorised as responders have responded on only one of the two measures. This would contradict the statement that they track each other. Please provide a cross-tabulation of response according SVR and TSS as well as a statistical assessment of the correlation between these two outcomes. Please comment on whether these data support the clinical expert advice that these outcomes "*track together*".

Response: Clinical advice received during the original submission for fedratinib in MF was that a combined endpoint of spleen or symptom response would be reflective of UK clinical practice. Therefore, these 2 endpoints have been added and included together in the model.

The figure below shows a scatter plot of the percentage reduction in spleen volume versus the percentage reduction in TSS at cycle 6 (from baseline). The fitted linear model (y ~ x) shows a positive correlation between variables, with a clear trend, which aligns with the clinical expert advice. The Spearman's rank correlation between variables is 0.304, further supporting the clinical expert advice.



B10. CS Table 42 and CS Table 43: Please clarify why the number of total patients varied between the two tables considering that both are measuring response at the same time point (end of cycle 6). If this is due to symptom evaluable population being those with a non-zero TSS score at baseline, then please clarify why the Ns in CS Table 43 (N=126 for fedratinib and N=65 for BAT) do not match the N's for the symptom evaluable population in CS Table 8 (N=121 for fedratinib and N=62 for BAT).

Response: We have taken the data from the CSR, using the tables from the CSR referenced in the CS. The primary analysis of symptom response was based on ITT population with non-zero TSS score at baseline (126/65); symptom evaluable population, on the other hand, had a more strict definition: All subjects who have been treated and have evaluable symptom assessments (i.e., non-zero total

symptom score) at baseline and at least one post baseline (121/62). This explains the difference in population sizes.

Duration of response

B11. PRIORITY CS Table 40 states that duration of response was explicitly included in the models used in TA386 and TA756 and implies that it was also included in the submitted model. However, duration of response was removed at technical engagement in TA756 (BMS, Addendum to NICE submission, p206 of Appraisal Consultation Committee papers). The EAG can find no reference to duration of response being part of the current model.

a) Please clarify if loss of response is included as an event in the model and if so what data are used to parametrise duration of response.

b) If time on treatment is being used as a proxy for duration of response, please justify this choice given that HRQoL is determined by response status and not treatment received.

c) The reasons for excluding duration of response in TA756 were related to limited data available and a lack of data using a combined definition of response using both spleen volume and symptoms. Given that durability of response data are provided using both spleen (CS Figure 6) and symptoms (CS Figure 8) in the CS and these data appear to be relatively mature, please comment on why duration of response using either spleen response (SVR ≥ 35%), symptoms response (TTS reduction ≥ 50%) or a combined definition cannot be included in the model using data from FREEDOM-2.

Response:

a) In the economic model, time on treatment is being used as a proxy for duration of response.

b) and c) There are several advantages to using time on treatment as a proxy for duration of response. These include:

- The resulting model is simpler and hence easier to understand than a model that includes both duration of treatment and duration of response curves.

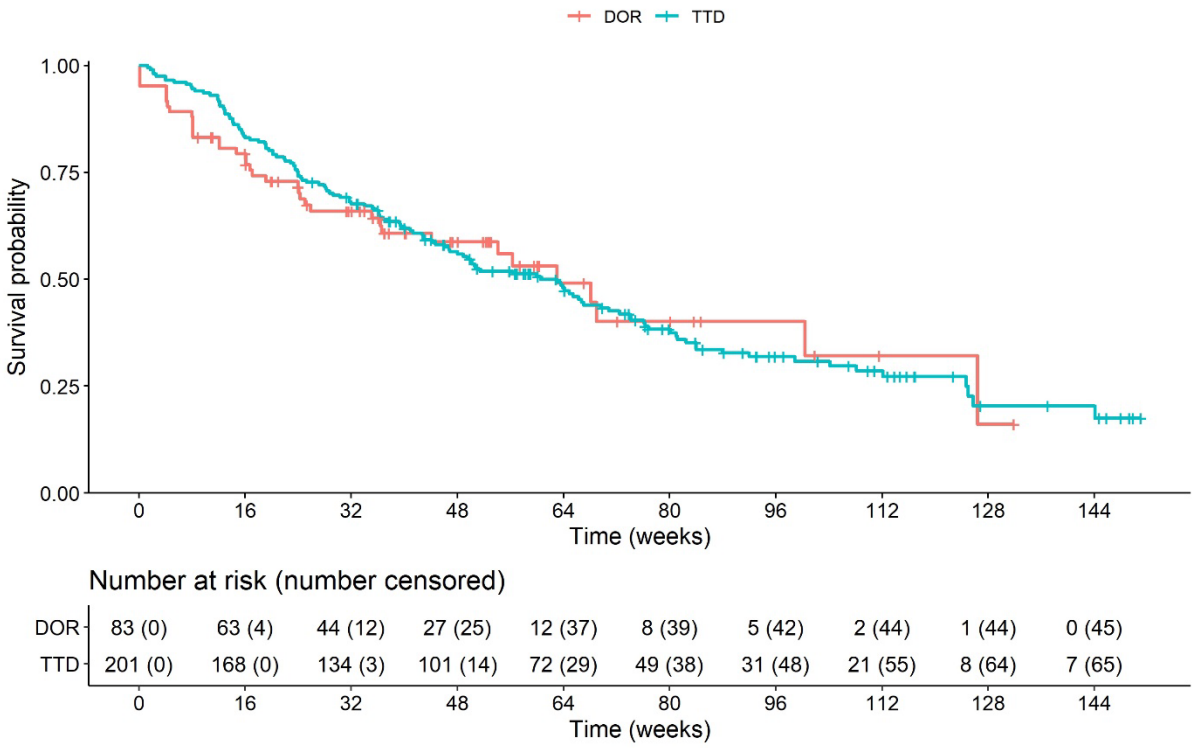
- In FREEDOM-2 treatment was given until lack of efficacy or intolerance. Hence, treatment discontinuation decisions will be influenced by the patient's HRQoL. Further, this approach ensures that there is consistency between the modelled costs of the treatments and their health benefits. For example, use of a separate duration of response curve could lead to patients receiving treatment with no clinical benefit or accruing the benefits of response after treatment discontinuation.
- The approach taken is consistent with the final approach used for the previous NICE appraisal of ruxolitinib (TA756).
- Use of time to treatment discontinuation allows for evidence from all patients to be used, not just the subset of patients who experienced a response. This means that larger sample sizes were available for statistical analyses, making them more robust.

B12. Plots of TTD by response status are provided in Appendix M.2 (CS Figures 23 to 25), but it is unclear whether these show time since the end of cycle 6, when response is assessed, or time since randomisation. Please clarify what the x-axis refers to in these plots.

Response: As per Appendix M, time to treatment discontinuation was "defined as the time from trial start to discontinuation of study treatment."

B13. If TTD is being used as a proxy for duration of response, then please provide plots comparing the Kaplan-Meier (KM) data for TTD and duration of response using end of cycle 6 (i.e., 6 months from baseline) as the starting point as this is the time response is defined in the model. The EAG notes that summary data for duration of response from end of cycle 6 are provided in the CSR, but no plots equivalent to CS Figures 6, 7 and 8 are provided.

Response: The figure below shows the Kaplan-Meier curve for TTD (all patients) overlaid with the Kaplan-Meier curve for durability of response (spleen volume or symptom) from the end of cycle 6.



The pooled duration of response curve has been derived from the following:

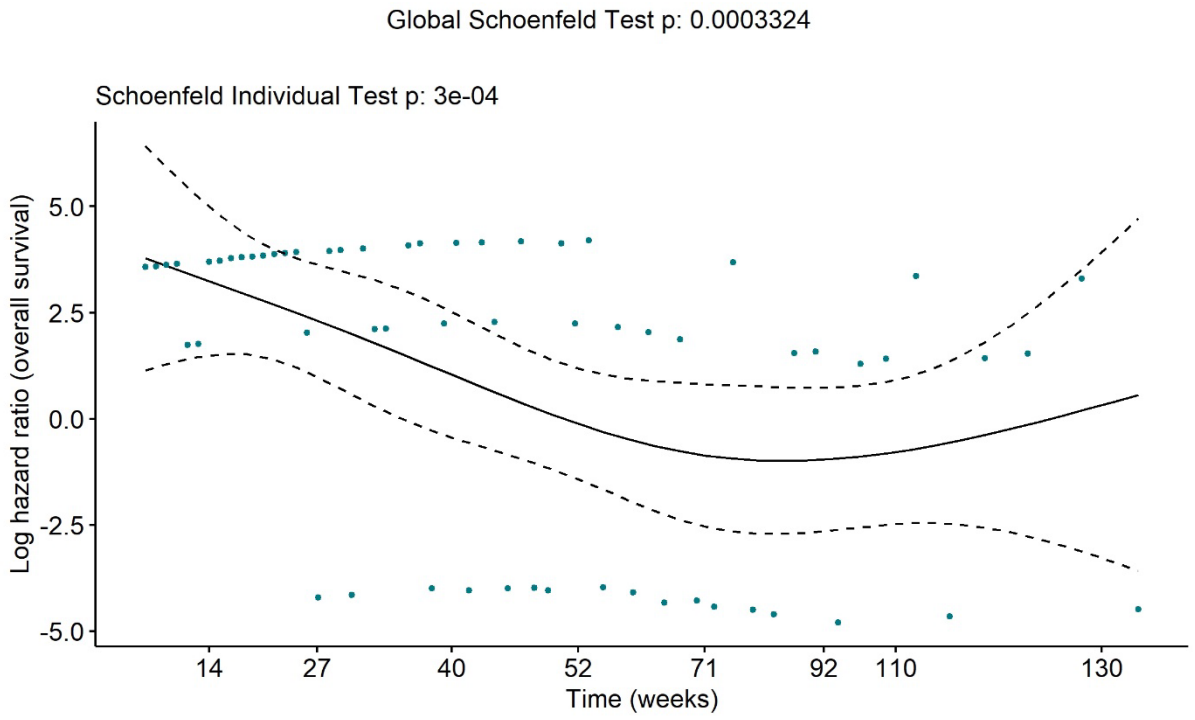
- Spleen volume response (SVR) time/event if the patient had SVR response but not symptom response at end of cycle 6
- Symptom response time/event if the patient had symptom response but not SVR response at end of cycle 6
- The longest follow-up time (and corresponding event/censor) for patients who had both an SVR and symptom response at end of cycle 6

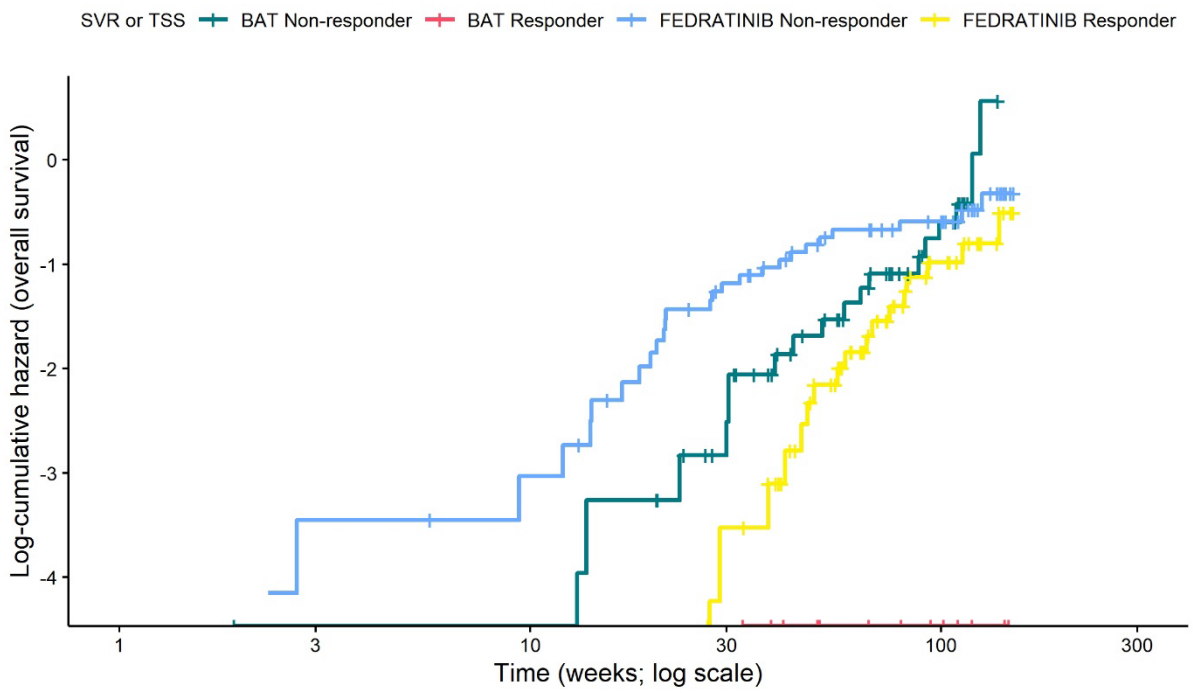
Survival curves

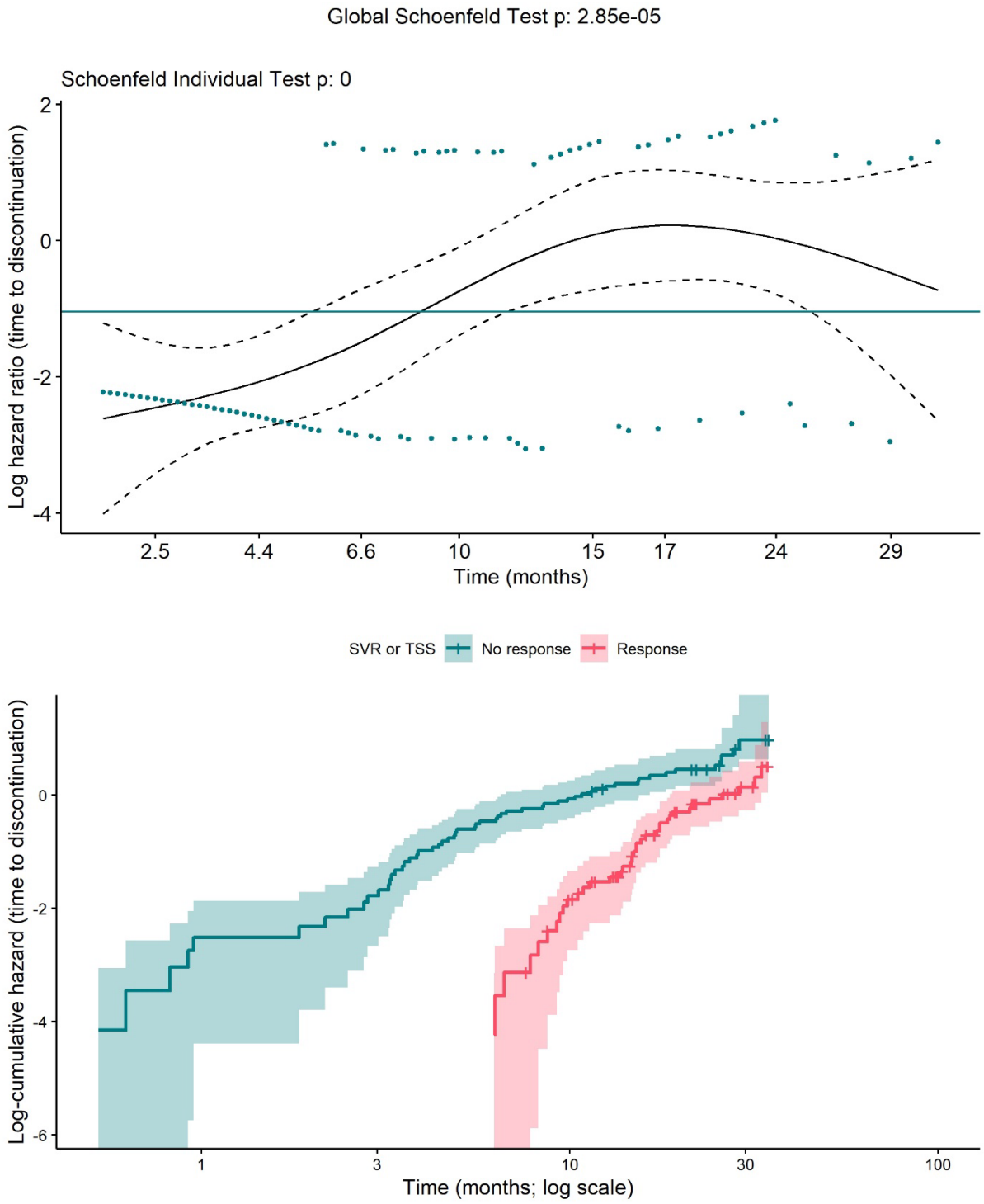
B14. Appendix M provides further details of parametric modelling and extrapolation for OS and TTD. Please provide the following extra details and describe how this information supports the decisions made:

- Nonparametric estimates of the hazard
- Assessment of proportional hazards (PH) and accelerated failure time (AFT) assumptions where appropriate (for models with a covariate for response status)
- Parameter estimates from these models (for the response parameter)

Response: As discussed in Appendix M, parametric modelling was driven by the clinical plausibility of extrapolations, for example ensuring that non-responders did not have better outcomes than responders. Given the small sample size, it was judged that hazard estimates would be too noisy to be informative. To test the proportional hazards assumption plots of Schoenfeld residuals, along with results of the global and individual Schoenfeld tests and log-log cumulative hazard plots were generated. These are displayed below for both overall survival (for both fedratinib and BAT by response status, albeit there were no deaths amongst BAT responders) and time to treatment discontinuation (for fedratinib by response status).


Global Schoenfeld Test p: 0.0003324
Schoenfeld Individual Test p: 3e-04
Log hazard ratio (overall survival)
5.0
2.5
0.0
-2.5
-5.0
14
27
40
52
71
92
110
130
Time (weeks)


SVR or TSS
BAT Non-responder
BAT Responder
FEDRATINIB Non-responder
FEDRATINIB Responder
Log-cumulative hazard (overall survival)
0
-1
-2
-3
-4
1
3
10
30
100
300
Time (weeks; log scale)



Collectively, these plots demonstrate that the proportional hazards assumption is violated for both overall survival and time to treatment discontinuation. Parameter estimates for the response parameter can be inferred from the survival parameter estimates in the submitted model, by comparing parameter estimates for the responder and non-responder subgroups (as for each survival model only 1 parameter, corresponding to the treatment effect, is varied).

B15. For the analysis of OS pooled across response status, separate models were fitted to each treatment arm. The CS Appendix M.1.1 states that *"The crossing of survival curves apparent in Figure 22 shows that it would not be appropriate to fit joint models (as this relies on a constant treatment effect assumption, which is violated when curves cross)."* Please provide further comment on this. In particular:

- Does the company think that the observed crossing of survival curves is to be expected (rather than being due to uncertainty and small sample size)? E.g. Fedratinib only showing improved OS towards the end of follow up

- If not then please reconsider this decision, fitting a model with covariate for treatment effect and showing all details required for model selection (see previous question)

Response: The crossing of the curves would not be expected in clinical practice as clinicians choose for patients to crossover from BAT to fedratinib in the FREEDOM-2 clinical trial. The observed crossing shows that the data violates the assumption of a constant treatment effect. Hence, even though we would anticipate a treatment effect, the small sample size combined with treatment crossover are such that it is not possible to reliably estimate a constant treatment effect. See also the response to B14.

B16. Please clarify what OS curve is applied to fedratinib non-responders when the stopping rule is implemented.

Response: A stopping rule is not implemented in either the base case or any scenario analyses, as this is not in line with what was done in the FREEDOM-2 clinical trial.

B17. Please run survival analysis on the SACT KM data for treatment duration and overall survival. Please provide incremental cost-effectiveness ratio (ICER) results when the appropriate curves from SACT are used in place of FREEDOM-2. Please

provide the SACT KM data and the parametric curves fitted to them in the updated model.

Response: We have added the SACT data to the model, with the option to choose it from the control sheet in the 'mortality' and 'discontinuation' sections. Of note, because the model base case assumes that clinical outcomes (TTD and OS) are equivalent between fedratinib and BAT, this assumption is used for the SACT analysis. Alternative assumptions were not explored as it would not be appropriate to compare outcomes from SACT with FREEDOM-2 due to the observed differences in OS.

Within-sample goodness of fit (Akaike's information criteria [AIC] and Bayesian information criteria [BIC]) values are provided in the table below and demonstrate that the exponential provides the best fit to both outcomes for both measures. Use of this distribution results in cost-savings of [redacted] for fedratinib.

Table 10. Akaike and Bayesian Information criteria for OS and TTD

	Overall survival		Time to treatment discontinuation	
Distribution	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	370.842	372.831	370.842	372.831
Generalised gamma	373.946	379.913	373.946	379.913
Gompertz	372.164	376.142	372.164	376.142
Log-logistic	372.232	376.210	372.232	376.210
Log-normal	372.259	376.237	372.259	376.237
Weibull	372.484	376.462	372.484	376.462

Key: AIC, Akaike's information criteria; BIC, Bayesian information criteria.

Definition of time to discontinuation in BAT

B18. PRIORITY Based on footnote 'a' to CS Table 26, the EAG understands that treatment duration for BAT is from day one of the first treatment cycle through to time of discontinuation or for patients who crossed over, the day before crossover.

a) How was TTD defined for patients having "*no treatment*" as BAT (CSR Table 14.3.1.1.2.1, N=[redacted] for No treatment)?

b) The EAG cannot see an obvious drop in the proportion on treatment for the BAT arm occurring around 6 months in Appendix M, Figure 25, or a large drop

in the numbers at risk in the KM data in the model. This suggests that the TTD curves for BAT include time on treatment for patients who crossed over to fedratinib. Please clarify how the TTD data for patients crossing over from BAT to fedratinib has been handled in the analyses that inform the TTD curves for the model. Please clarify if patients crossing over to fedratinib after cycle 6 were censored at the time of crossover for the purposes of estimating TTD or whether instead all of these patients were recorded as having a TTD of the day before their crossover (i.e., around 6-7 months). Or alternatively were they considered to remain on treatment until discontinuing fedratinib for the purposes of the TTD analysis?

c) If patients in the BAT arm could receive more than one sequential BAT treatment (see Question A12), was TTD measured until discontinuation of the first BAT treatment only, or until discontinuation of the last BAT treatment?

d) It is stated that "*Subjects were allowed to continue study treatment until occurrence of unacceptable toxicity, lack of therapeutic effect, progression of disease according to the IWG-MRT 2013 criteria or withdrawal of consent*," and "*Subjects on the BAT arm were treated according to local prescribing information*." (CSR, page 31) Were all therapies allowed within BAT able to be given until unacceptable toxicity or disease progression or were any required to be given for a maximum duration specified in their SmPC?

e) Please provide the median (and 95% CI) TTD for the fedratinib and BAT arms.

Response:

a) The participants not receiving any treatments in the BAT arm are considered to have the same TTD as the other patients in the BAT basket. Only 1 TTD, for the whole BAT basket was generated by the FREEDOM-2 clinical trial, and no individual TTD by treatment were available.

b) In the model, we have not defined treatment crossover from BAT to fedratinib as treatment discontinuation. The TTD curve that we derived matched Table 14.1.3.1 in the CSR supplementary table materials (with respect to the number of events observed). There were 46 patients who crossed over from

the BAT arm to fedratinib. Of these 46 patients, their time on BAT is summarised as follows:

	Mean (SD)	Median	Number of patients
Time on BAT (days)	[redacted]	[redacted]	46

Of the 46 patients, 21 experienced a treatment discontinuation event after crossing to fedratinib. For the 25 patients who did not yet discontinue treatment on fedratinib, their discontinuation date was set to be the study end date, and these patients were censored. A naive summary of all these patients (no adjustments for censoring) is given below.

	Mean (SD)	Median	Number of patients
Time on fedratinib (days)	[redacted]	[redacted]	46

Note that if median time on fedratinib is adjusted for censoring there is an expected median of around [redacted] days.

c) In the economic model TTD was measured until the discontinuation of the first treatment. The patient then moves onto the subsequent line of therapy.

d) In the model, all the therapies are given until time to treatment discontinuation, as per the CSR.

e) The median time to treatment discontinuation is [redacted] weeks for fedratinib and [redacted] weeks for BAT.

B19. When describing data collection for treatment exposure, CSR page 74 states, "*If one medication is prevalent in BAT arm (e.g., 50% subjects in BAT arm take the same medication), a detailed summary for that medication will be conducted using the same variables listed above*." Please clarify whether duration of treatment was collected in the same manner for fedratinib and for all components of BAT or only those components received by more than 50% of BAT patients.

Response:

We could not locate the statement that the EAG mentioned on page 74 of the CSR, or in any other part of the document, so we were not able to give a response without further clarification regarding where this statement has been taken from.

Utilities

B20. Please clarify if MF-8D was collected in FREEDOM-2 or derived from other data collected in the trial. The EAG can find no mention of this outcome in the study protocol or CSR. If scores were derived from other data collected (e.g., MFSAF and/or EORTC QLQ-C30), please provide details of how MF-8D utility values were obtained from the data collected including: a) the versions of any questionnaires used, the dimensions from each scale which contributed to the MF-8D, b) the publication reporting the derivation of the preference based measure, and c) a brief description of the valuation method used to obtain utility values to enable assessment against the NICE reference case.

Response: MF-8D was not collected in FREEDOM-2, so EORTC QLQ-C30 v3.0 and MFSAF v4.0 data from FREEDOM-2 were used to derive MF-8D using methods described by Mukuria et al. (2015).[8] The methods described by Mukuria et al. (2015) use EORTC QLQ-C30 v3.0 and MFSAF v2.0. The table below outlines the questionnaire responses used in the method described by Mukuria et al. (2015) and the questionnaire responses used for the FREEDOM-2 derivation given the versions of MFSAF differed.

Table 11. Comparison of questionnaire responses described by Mukuria et al. (2015) and responses used for the FREEDOM-2 derivation

MF-8D dimension	Mukuria et al. (2015) method based on	FREEDOM-2 derivation
Physical functioning	EORTC QLQ-C30 (v3.0) – 1) do you have any trouble taking a long walk? 2) do you have any trouble taking a short walk outside of the house?	Same as Mukuria et al. (2015)
Emotional functioning	EORTC QLQ-C30 (v3.0) – during the past week, did you worry?	Same as Mukuria et al. (2015)
Fatigue	EORTC QLQ-C30 (v3.0) – 1) during the past week, were you tied? 2) during the past week, were you short of breath?	Same as Mukuria et al. (2015)
Itchiness	MFSAF (v2.0) – how severe was your worst itchiness due to MF?	MFSAF (v4.0) – how severe was your worst itching?

MF-8D dimension	Mukuria et al. (2015) method based on	FREEDOM-2 derivation
Pain under ribs on the left side	MFSAF (v2.0) – how severe was your worst pain under the ribs on the left side due to MF?	MFSAF (v4.0) – how severe was the worst pain under the ribs on the left side?
Abdominal discomfort	MFSAF (v2.0) – how severe was your worst abdominal discomfort (feel uncomfortable, pressure or bloating) due to MF?	MFSAF (v4.0) – how severe was your worst abdominal discomfort (feeling pressure or bloating)?
Bone or muscle pain	MFSAF (v2.0) – how severe was your worst bone or muscle pain due to MF (diffuse not joint or arthritis pain)?	MFSAF (v4.0) – how severe was your worst bone pain (not joint or arthritis pain)?
Night sweats	MFSAF (v2.0) – how severe were your worst night sweats (or feeling hot or flushed) due to MF?	MFSAF (v4.0) – how severe were your worst night sweats (or feeling hot or flushed)?

To derive the MF-8D utility estimates, responses to the EORTC QLQ-C30 and MFSAF questionnaires in FREEDOM-2 were merged based on the time of completion. At each visit, all patients who completed an EORTC QLQ-C30 questionnaire also completed an MFSAF questionnaire. Therefore, it was possible to match all observations of EORTC QLQ-C30 with an MFSAF questionnaire. EORTC QLQ-C30 and MFSAF questionnaires were not always completed on the same day (for a given patient); therefore, a cutoff of 2 weeks was applied to match the assessments. MF-8D utility estimates were then derived as per Table 4 of Mukuria et al. (2015) using patient responses to the questions outlined in the table above.

B21. The CS states (p107) that MF-8D is considered the "*most appropriate*" HRQoL measure and that it is "*more sensitive to changes in the QOL of people with myelofibrosis because the MF-8D is better able to estimate QOL of people with myelofibrosis compared with other instruments such as the EQ-5D*." However, the NICE reference case requires the EQ-5D to be used except in situations where there is evidence to demonstrate that it is inappropriate. Please also provide a fuller justification of why EQ-5D is not appropriate in this case as per section 4.3.10 of the NICE methods guide. Please provide a scenario analysis using EQ-5D outcomes from the FREEDOM-2 trial in place of the MF-8D values within the model.

Response: EQ-5D may not be appropriate for all patient groups or all populations, and it was settled in the fedratinib original NICE submission that MF-8D would be the most relevant instrument to quantify HRQoL in MF. For example, Section 4.3.3.13 (p176) of the original Evidence Review Group (ERG) report stated that:

"*The ERG considers the use of the MF-8D[46] in the base-case to be generally appropriate and in line with TA386[13] given psychometric properties of the EQ-5D[44, 47] in this patient population.*"

Limitations of generic measures in disease areas such as oncology are widely recognised; for example, psychometric analyses have indicated that the performance of EQ-5D in myelofibrosis (MF) is not ideal. Psychometric analyses of the performance of the EORTC QLQ-C30 against MF measures indicate that the EORTC QLQ-C30 captures functioning and some generic symptom problems. However, EORTC QLQ-C30 does not cover MF-specific symptoms (such as weight loss, itching, and night sweats) and is not as responsive as the MFSAF over time. The myelofibrosis 8 dimension (MF-8D) was developed as a condition specific preference-based measure from the MFSAF version 2.0 and the EORTC QLQ-C30 that captures the HRQoL of patients with MF and overcomes some of the concerns related to using the EQ-5D and EORTC QLQ-C30.

B22. Section B.3.4.1.1 Utility regression in the model. Please provide details on the model selection process that resulted in the final regression model summarised in CS Table 53, justifying the final choice of model.

a) The text describes regression models both with and without gender, but coefficients are only presented in CS Table 53 for treatment response and baseline utility. Please provide results for the model with gender as a covariate and clarify why the final model did not include gender as a covariate.

b) Please also clarify the model selection with regards to exclusion of the other listed covariates. In particular, please clarify why age and sex are not included in the final model, but later (CS section B.3.4.1.4.) age specific utilities values are predicted for male and female patients.

c) CS Table 53: In the utility regression does the "*responder status*" covariate apply to those who responded at 6 months or is it based on whether they are

classed as a responder or non-responder on the visit where HRQoL was measured.

d) CS Tables 53 and CS Table 56: The information on the regression in CS Table 53 suggests that treatment allocation was not a covariate in the regression. If this is the case, then please clarify why in CS Table 56 patients having a non-response to fedratinib are assumed to have a utility increase of 0.052 versus baseline whereas patients having a non-response to BAT are assumed to have no change from baseline. Was this an assumption applied in the model rather than an outcome of the regression?

e) CS Table 56, please also clarify in the rows labelled "*JAK response*" and "*JAK non-response*" apply only to the fedratinib arm and not to patients having ruxolitinib within BAT.

Response:

a) Utility regression models were analysed with and without gender (for each response definition). The regression models excluding gender provided the best fit to the data based on lower AIC and BIC statistics. Additionally, gender was not statistically significant when included in the regression analyses (see table below). Therefore, the final model excluded gender based on the principle of parsimony.

Table 12. Utility regression estimates

Coefficient	Coefficient subcategory	Estimate	Standard error	*P* value
Spleen and/or symptom response model				
Intercept	NA	0.369	0.031	< 0.001
Baseline MF-8D utility	NA	0.499	0.044	< 0.001
Response status	Non-responder		Reference	
	Spleen and/or symptom responder	0.115	0.018	< 0.001
Sex	Female		Reference	
	Male	0.016	0.019	0.398
Spleen response model				
Intercept	NA	0.394	0.033	< 0.001

Coefficient	Coefficient subcategory	Estimate	Standard error	*P* value
Baseline MF-8D utility	NA	0.506	0.047	< 0.001
Response status	Non-responder		Reference	
	Spleen responder	0.073	0.022	0.001
Sex	Female		Reference	
	Male	0.021	0.020	0.309
Symptom response model				
Intercept	NA	0.382	0.030	< 0.001
Baseline MF-8D utility	NA	0.501	0.043	< 0.001
Response status	Non-responder		Reference	
	Symptom responder	0.134	0.020	< 0.001
Sex	Female		Reference	
	Male	0.013	0.019	0.488

b) MF-8D values were assessed in exploratory analyses for the following patient characteristics: age, sex, race, ECOG PS, myelofibrosis diagnosis, haemoglobin count, platelet count. Results showed a possible correlation between sex and MF-8D utility and ECOG PS and MF-8D utility. Both covariates (sex and ECOG PS) were explored in regression models in addition to baseline utility and response status, but neither covariate was found to be statistically significant. Additionally, including these covariates did not improve model fit. As such, sex and ECOG PS were not included in the final model.

   Although utility estimates are presented separately for male and female patients in Table 56, no adjustment was made based on sex (i.e., utility values in the model are the same for male and female patients).

   An age-gender related utility adjustment was applied in the cost-effectiveness model to account for the natural decline in QOL over time.

c) Responder status is based on whether a patient was a responder at the end of cycle 6 rather than the visit where HRQoL was measured.

d) Table 56 reflects the utility values used in the model rather than the outputs of the regression which are reported in Table 53.

e) It is the correct interpretation that "*JAK response*" and "*JAK non-response*" apply only to the fedratinib arm, and do not apply to the BAT arm.

B23. B.3.4.1.2. Utility results. Please clarify the following:

a) CS Table 54. Why is the median (range) not reported for male and female?

b) CS states "*The pooled baseline (all) is a weighted average of the baseline utility for males and females*." Is the pooled baseline the mean for all patients? If not please clarify how the weighted average was calculated.

c) Please provide summaries (mean values and also histograms showing the distribution) of MF-8D by responder status, separately by sex and pooled.

d) Please clarify the rationale for using the regression modelling approach (Question B22 above) rather than the actual MF-8D values for specific subgroups of relevance to the model.

Response:

a) Median (range) was not reported at the time. Median (range) baseline MF-8D utility for male patients was 0.741 (0.197-0.993). Median (range) baseline MF-8D utility for female patients was 0.574 (0.134-0.993).

b) The *"pooled baseline (all)"* results represent the mean (SD) and median (range) utility values for all patients where baseline values were available.

c) Descriptive summarises of postbaseline MF-8D utility by responder status, separately by sex and pooled.

    a. Spleen and/or symptom responder

Table 13. Responder status (spleen and/or symptom)

Responder status (spleen and/or symptom)	Sex	Number of patients	Number of observations	Mean (SD)	Median (range)
Yes	Pooled	94	1,341	0.824 (0.149)	0.863 (0.200-0.993)
	Male	50	725	0.858 (0.135)	0.888 (0.200-0.993)
	Female	**44**	**616**	**0.785 (0.154)**	0.808 (0.265-0.993)

Responder status (spleen and/or symptom)	Sex	Number of patients	Number of observations	Mean (SD)	Median (range)
No	Pooled	114	928	0.716 (0.203)	0.754 (−1.077-0.993)
	Male	58	481	0.750 (0.218)	**0.806 (−1.077-0.993)**
	Female	56	447	0.680 (0.180)	**0.707 (0.134-0.993)**

Figure 2. Histogram of MF-8D by spleen and/or symptom responder status

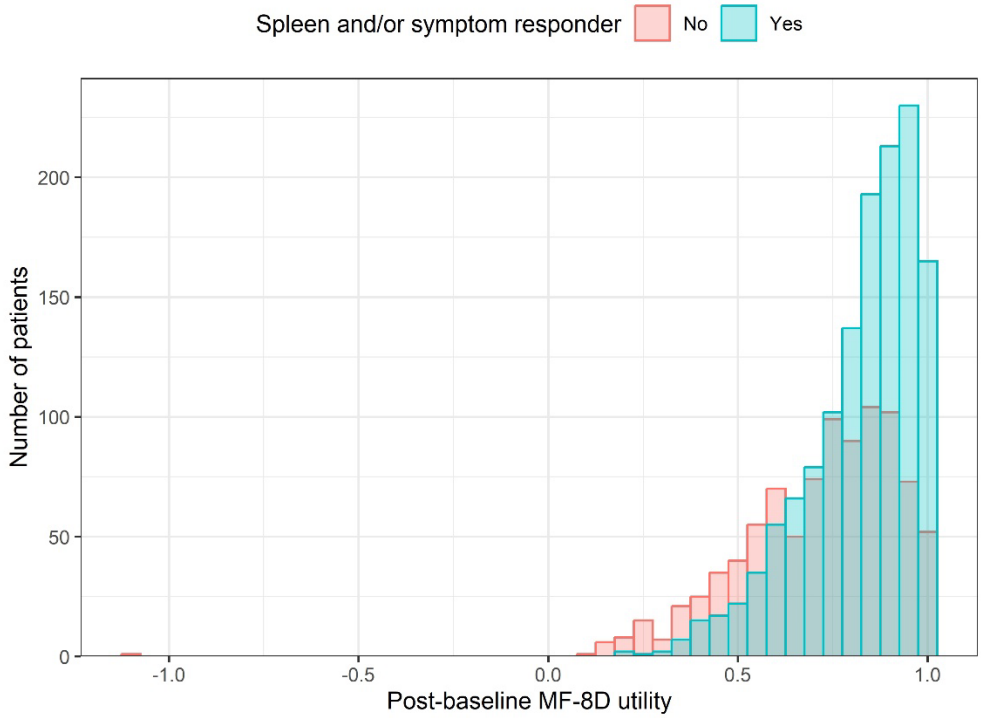
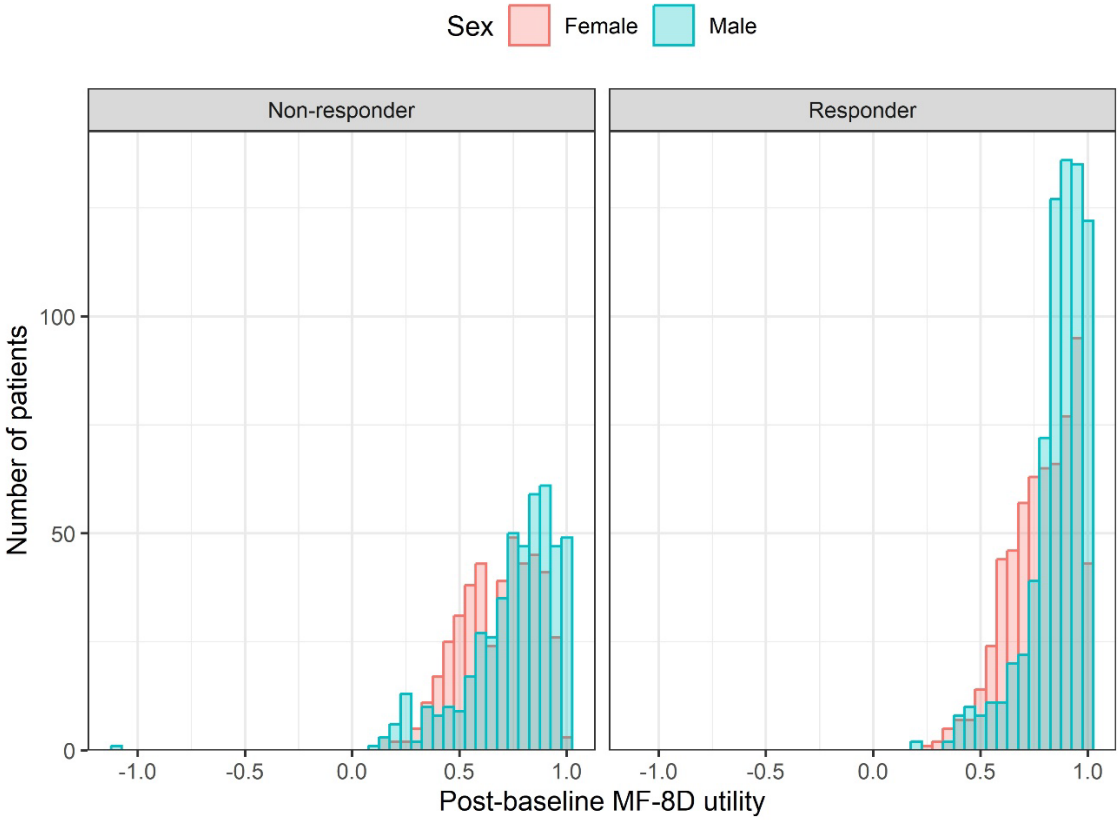


Figure 3. Histogram of MF-8D by spleen and/or symptom status and sex



b. Spleen responder

Table 14. Responder status (spleen)

Responder status (spleen)	Sex	Number of patients	Number of observations	Mean (SD)	Median (range)
Yes	Pooled	58	855	0.807 (0.156)	0.847 (0.265, 0.993)
	Male	29	442	0.852 (0.137)	0.888 (0.362, 0.993)
	Female	29	413	0.760 (0.162)	0.769 (0.265, 0.993)
No	Pooled	139	1,414	0.763 (0.193)	0.812 (−1.077, 0.993)
	Male	75	764	0.793 (0.198)	0.849 (−1.077, 0.993)
	Female	64	650	0.729 (0.179)	0.762 (0.134, 0.993)

Figure 4. Histogram of MF-8D by spleen responder status

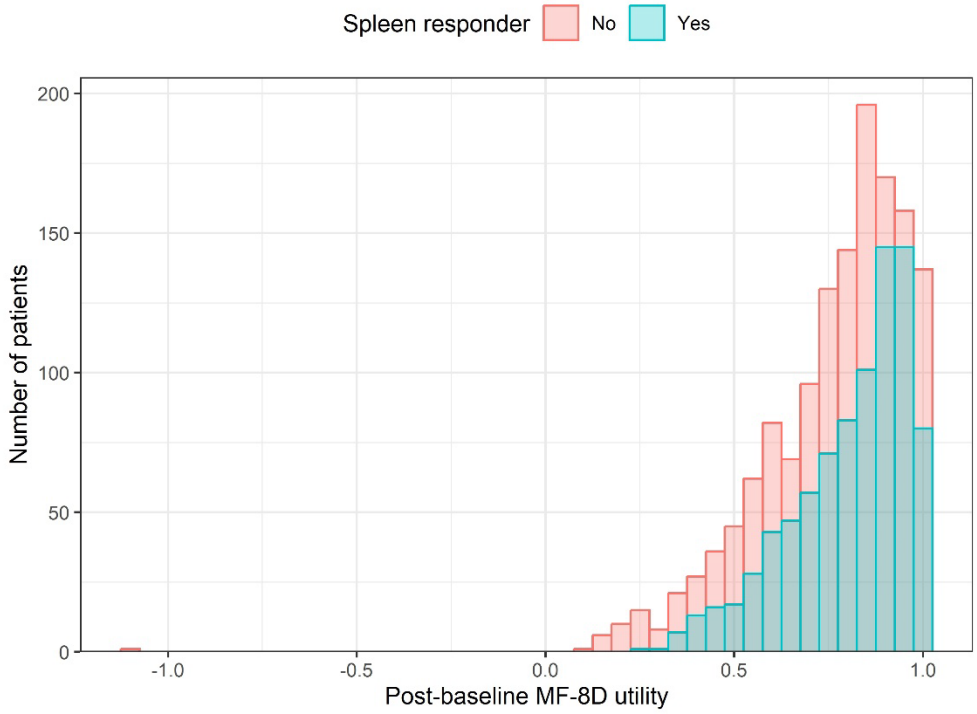
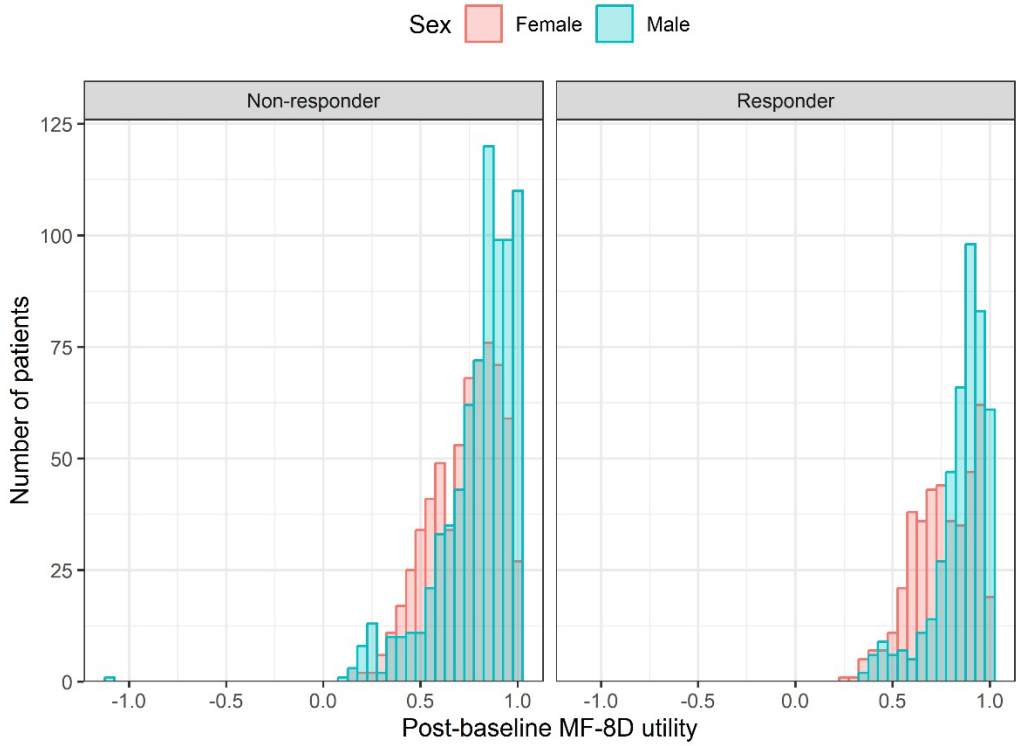


Figure 5. Histogram of MF-8D by spleen responder status and sex



c. Symptom responder

Table 15. Responder status (symptom)

Responder status (symptom)	Sex	Number of patients	Number of observations	Mean (SD)	Median (range)
Yes	Pooled	65	920	0.857 (0.125)	0.883 (0.200, 0.993)
	Male	36	544	0.879 (0.115)	0.909 (0.200, 0.993)
	Female	29	376	0.824 (0.131)	0.847 (0.295, 0.993)
No	Pooled	141	1,349	0.728 (0.194)	0.760 (−1.077, 0.993)
	Male	71	662	0.762 (0.206)	0.820 (−1.077, 0.993)
	Female	70	687	0.695 (0.177)	0.710 (0.134, 0.993)

Figure 6. Histogram of MF-8D by symptom responder status

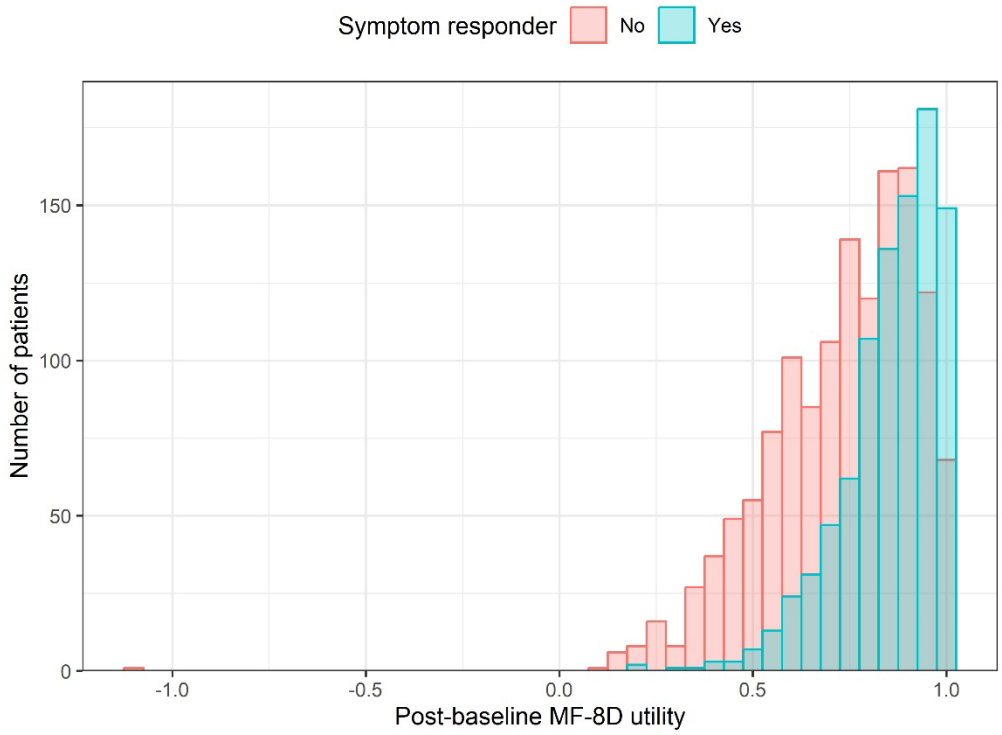
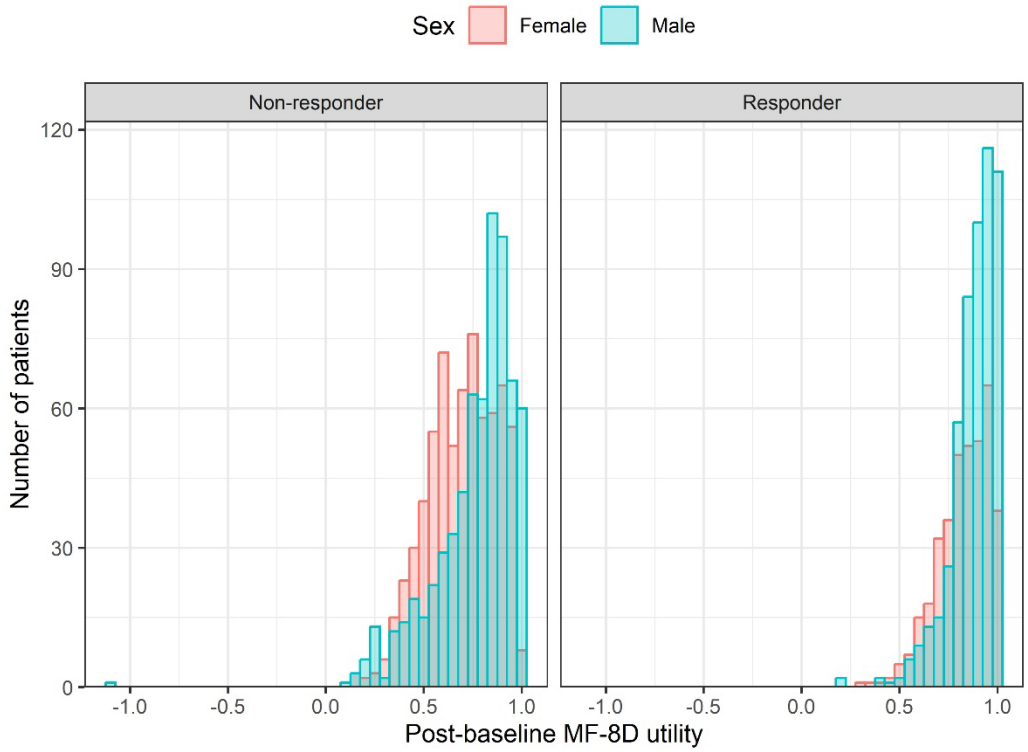


Figure 7. Histogram of MF-8D by spleen responder status and sex



d) Mixed effects regression modelling of MF-8D was preferred over actual MF-8D values for the following reasons:

   a. Regression models can simultaneously account for multiple covariates without compromising on sample size

   b. The regression models account for differences in baseline utility

   c. Mixed effects regression was used which accounts for multiple observations from the same patient

Ruxolitinib costs accounting for dose distribution and dose modifications

B24. PRIORITY Additional information is required to understand how the data in CS Table 63 on dosage of ruxolitinib have been derived. Please respond to each of the following queries:

a) The CS states, "*The distribution of ruxolitinib doses provided in Table 62 is based on the initial dose and the doses (in mg) received at the end of each*

cycle until cycle 6." Please include a sheet in the model showing the calculation of the distribution in CS Table 63 from the data in CS Table 61 and the initial doses.

b) The CS states (p116) that "*patients can receive more than one dose of ruxolitinib per cycle; hence, proportions can exceed 100%."* However the data in CS Table 61 are described as reporting doses at the end of each cycle, and therefore only a single dose should be reported per patient. The CS also states, "*To estimate the proportion of patients receiving each dose strength (i.e., 5 mg, 10 mg, 15 mg and so on), the total number of patients receiving the dose strength was summed across the 6 cycles and was then divided by the total number of patients who received an initial dose*." This method does not appear to adjust for time spent on each dose. Please clarify how the data in CS Table 61 have been derived, with particular reference to the time points that dosages were recorded and how time spent on each dose is accounted for within the proportions. We would suggest that this is best explained by showing the calculations made using the deidentified patient-level data or showing equivalent calculations for a dummy example dataset.

c) Please provide a table of showing the number of patient-weeks (or patient-years) spent on each dose across the BAT cohort.

d) Please clarify how the data in CS Table 63 correspond to a mean dose of 24.1 mg per patient and describe what timepoint or time-period this mean dose has been estimated for with reference to where these data are presented in the CSR.

Response:

a) We have added the sheet in the model and linked it to the drug cost calculations. The newly added sheet is called "Ruxolitinib detailed costing."

b) The data presented in Table 61 are the cumulative number of doses received within each cycle. Evidence on the time spent on each dose is not available. It is not unreasonable to assume that when a patient changes doses mid-cycle there will be wastage as the old dose can no longer be used.

c) Patient-weeks or patient-years were not available from the CSR for these types of data. The information presented in the CS Table 61 refers to the first 6 cycles on treatment. A cycle of treatment was 4 weeks (28 days cycle). Therefore, the first 6 cycles presented in the model account for 24 weeks.

d) The mean dose was retrieved from Table 14.3.1.1.2.2 in the CSR supplemental material. This is based on the initial dose received by patients in the FREEDOM-2 clinical trial. To account for dose missed or postponed, a RDI is applied to ruxolitinib if the option to calculate ruxolitinib costs using the mean dosage is chosen.

B25. PRIORITY CS, page 113 states "*Wastage is also included in the model to account for frequent dose adjustments on ruxolitinib, which results in the remaining tablets within a pack being discarded*." Please clarify whether the company is assuming that patients would be prescribed a whole cycle of treatment at the start of each cycle, with all of that medication being discarded if a dose adjustment is made mid-cycle. Please comment on whether this reflects the process used to manage dose adjustments and drug wastage in clinical practice or whether this is being driven by the FREEDOM-2 trial protocol, for example procedures that require patients to return unused drugs each cycle to establish compliance (see CSR page 67). Please also comment on whether these dose changes in FREEDOM-2 are likely to be driven by adverse event monitoring procedures that require mid-cycle FBC checks that may not occur in clinical practice.

Response: Ruxolitinib tablets are available as packs of 56. The ruxolitinib wastage approach in the model assumes that when a patient changes dose at some point during the cycle, the remaining pack is discarded and a new pack prescribed. This approach is intended to reflect clinical practice, as when a new dose is used, tablets from the old dose are unlikely to be used.

B26. Model, 'Drug Costs' D335:F341. Please respond to the following queries:

a) It seems row 320 (ruxolitinib 5 mg) is missing from the calculations at E336. Please clarify why this is the case.

b) The EAG understands that these rows are to convert the daily doses into proportions according to the available strengths for ruxolitinib (i.e., 5, 10, 15,

and 20 mg). Please clarify why ruxolitinib 30 mg + 5 mg was included as a means of achieving a 35 mg dose when 30 mg is not a strength available according to the SmPC. Please consider replacing this with a 20 mg and 15 mg combination.

c) It's also the EAG's understanding that column F weighs the proportions to unify all dosing to be twice daily. Please clarify why F340 equals D340+E340 instead of D340+E340/2.

d) Please also check the calculations related to the 30 mg tablet strength in row 184 which appears inconsistent with the previous and subsequent rows.

Response:

a) This was omitted by mistake; it has now been included.

b) This has been changed in the model, where 3.3% of patients will go onto receiving 15 mg once daily and 3.3% 20 mg once daily to amount to 35 mg.

c) This calculation has been set up differently because none of the patients are receiving 30 mg twice daily.

d) Thank you for checking. All the drug strengths for the ruxolitinib aside from the 5 mg strength cost the same. In the model, the cost of any vial beyond 20 mg is assumed to be the same as the 20 mg. Therefore, we have amended the calculation to reflect this.

Dose modifications for fedratinib

B27. The SmPC for fedratinib describes dose adjustments for the management of AEs. The EAG notes that CS Table 38 shows a higher proportion of patients in the fedratinib arm had ≥ 1 TEAE leading to dose modification, but wastage due to dose modifications is only discussed in the CS in relation to ruxolitinib. Please clarify what wastage is assumed in the model for patients having dose adjustments on fedratinib and consider amending the model to incorporate wastage due to dose modification

in a consistent manner across patients receiving ruxolitinib and patients receiving fedratinib

Response: In the model, wastage for fedratinib is assumed to be 0%. Patients are given ruxolitinib based on a distribution of doses, which accounts for wastage, whereas this is not the case for fedratinib as there is only a single tablet strength. Therefore, the wastage for fedratinib has been set up separately. Dose modification is captured by the use of relative dose intensity.

Resource use

B28. Please clarify whether assessment of response by MRI is assumed every 6 cycles in the model? If it is not included, please clarify how patients are assessed as progressing on treatment. This is important as patients discontinued study drug on progression in FREEDOM-2 and therefore TTD will be dependent on how often patients are assessed for disease progression.

Response: As noted in the company submission, healthcare resource use data were not available from FREEDOM-2. Instead, this evidence was taken from several sources. Resource use was based on visits to healthcare providers, such as outpatient visits, instead of microcosting individual resource elements. Hence use of MRI for response assessment will be implicitly captured within the resource use estimates. This approach is consistent with the previous NICE submission for fedratinib (TA756).

B29. Please clarify why the reference cost for 'Deliver Subsequent Elements of a Chemotherapy Cycle' has been applied for interferon alpha. Is this treatment classed as chemotherapy? Is it usually administered in a day case hospital setting or is it usually given via homecare, primary care or outpatient procedure?

Response: The administration cost for interferon has been amended in the model to reflect "Injection (SC)". The cost of SC injection is assumed to be the same as a GP visit, as NHS guidance on administration of interferon alpha noted that this immunotherapy could be given at the GP.

B30. Please clarify why the reference cost for 'Deliver Subsequent Elements of a Chemotherapy Cycle' has been applied for interferon alpha. Is this treatment classed

as chemotherapy? Is it usually administered in a day case hospital setting or is it usually given via homecare, primary care or outpatient procedure?

Response: Please see response to B29.

Supportive care/ palliative care

B31. PRIORITY. The model (Model Structure sheet C98:D102) describes the possibility for patients discontinuing fedratinib to transition to either BAT (post fedratinib) or supportive care. The model seems to suggest that the proportion of non-responders to fedratinib having BAT after fedratinib is 33.3% and it is based on the proportion currently receiving treatment after ruxolitinib from Haematological Malignancy Research Network (HMRN) (Control sheet, C249:L249). However the proportion of responders to fedratinib having BAT when they discontinue fedratinib is 66.7% in the model with the source described as "*assumption*" (Control sheet C252:L252), but the EAG cannot identify where either of these values are discussed in the CS. Please clarify how these proportions were estimated and what justification there is for assuming a higher proportion remain on BAT after fedratinib for responders versus non-responders.

Response: Post-fedratinib transitions to BAT, supportive care, and death were informed by inputs from clinical opinion received during the original submission. This was not updated as part of the new FREEDOM-2 data.

Clinical opinion for post-fedratinib transitions were that, for non-responders, 33.3% would be expected to continue to BAT after fedratinib, with 66.7% transitioning to supportive care. For responders, it was estimated that 66.7% would transition to BAT after fedratinib, with 33.3% transitioning to supportive care. For those patients who receive BAT after fedratinib, the proportion of remaining time alive spent in supportive care versus BAT was estimated to be 40.4% for both responders and non-responders, based on the ratio of undiscounted life-years between BAT and supportive care observed in the BAT arm results. The 35.1% was a typo in the model and has been replaced by 40.4%.

B32. PRIORITY When describing worsening quality of life for patients having supportive care, CS Table 39 describes supportive care as applying to the last 30% of time on BAT. A proportion of 35% appears to be applied in the model for BAT-post

fedratinib (Control sheet, J258:J259) but the EAG cannot identify where this is described in the CS. The model states (control sheet row 256) that this is "*Based on the ratio of predicted undiscounted LYs in the BAT arm between BAT and supportive care, approximately 40.4% of remaining life expectancy is spent in supportive care, after receiving BAT*." The proportion of 40.4% appears to be calculated by dividing life-years (LYs) spent in supportive care by total LYs in the BAT arm from the model Results sheet. Please describe how time on supportive care is determined in both arms. Please describe whether this results in equal or differential time on supportive care and, if differential time is spent in supportive care, discuss whether this reflects clinical practice.

Response: For patients in the BAT arm, time spent in supportive care is the difference between time spent receiving BAT and time to mortality. This corresponds to 40.4% of the life-years for patients receiving BAT in the base case. To ensure similarity, patients who receive BAT after fedratinib are modelled as spending 40.4% of their remaining life (after discontinuing fedratinib) on supportive care, with the remaining time receiving BAT. Of note, for patients who do not receive BAT after fedratinib, their time spent in supportive care is the difference between time spent receiving fedratinib and time to mortality.

B33. CS Table 39: This table describes transitions to 'palliative care' in the last row, but only transitions to supportive care are described in the Model Structure sheet of the Excel file. In addition, the definition of palliative care (last 8 weeks of life, CS Table 39) and supportive care (last 30% of time on BAT, CS Table 39) do not appear to agree. The EAG understands that the palliative care state was removed from the model in TA756 after technical engagement and replaced with a one-off end-of-life cost (BMS, Addendum to NICE submission, p206 of Appraisal Consultation Committee papers; also stated in page 88 of current CS). Please clarify if both palliative care and supportive care are applied in the model, or whether the text referring to palliative care is no longer relevant. If so, then please also clarify if the text referring to utilities for palliative care in CS Table 40 and in the Text above CS Table 59, is meant to refer to utilities for supportive care.

Response: Palliative care costs are the same as end-of-life costs, which are incurred in the model when patients reach the Death health state. It is not the same as the Supportive Care health state, which is an additional health state in the model

meant to reflect the state the patients are in after they spent time in BAT and progressed. Therefore, both terms are used in the model, but only supportive care is a health state. The health utilities in CS Table 59 should refer to supportive care.

Adverse events

B34. CS Table 45: Please confirm if the data in CS Table 45 have been taken from Table 8.6.3-1 of the CSR. If so, then please clarify why not all AEs in Table 8.6.3-1 are included in CS Table 45.

Response:

Only non haematological adverse events (AEs) grade ≥ 3 were explicitly modelled in the NICE submission, because the impacts of thrombocytopenia, anaemia, and neutropenia (common haematological AEs in MF) on costs and utilities are assumed to be already captured by the model, with the costs of haematological AEs being counted in resource use estimates; and the impact on utilities of such AEs are assumed to be captured within the health state utility values. Therefore those AEs, despite being included in table 8.6.3-1 of the CSR, were not included in CS Table 45

B35. Please clarify how AEs have been incorporated for BAT after fedratinib and whether these are assumed to be equivalent to the AEs for BAT as a comparator or whether they differ (for either costs, utilities or both). The EAG believes that an inconsistent approach has been taken for AEs in patients having BAT after fedratinib with costs included but utility decrements not included. If this is the case, then please reconsider and amend or justify the approach taken.

Response:

In the model, it is assumed that the incidence of the AE for ‘BAT (after fedratinib)’ is the same as the incidence for ’BAT (as comparator)’. The formula in the model used to calculate AE disutilities has been updated to reflect this.

B36. Please provide a scenario where the incidence of AEs is based on Grade 3/4 AEs experienced in the first 6 cycles of treatment, and where cost and utility implications of AEs are applied upfront to all patients according to allocated treatment arm. The EAG’s rationale for requesting this is that it allows AEs to be estimated in a period where treatment exposure is similar across arms and removes

the need to estimate exposure-adjusted incidence rates, which requires an assumption that AEs occur at a constant rate which may not be true.

Response: It was not possible to perform this analysis given the time constraints for responding to the clarification questions. However, it is expected that the impact of such an analysis would be negligible.

B37. Transitions to acute myeloid leukaemia (AML). The CS states (p96) that "*There was no observed transformation to AML in FREEDOM-2. Nevertheless, this was included in the model AEs list to reflect the potentiality that myelofibrosis may also transform to AML. The incidence for transformation to AML was taken from the NICE 2016 TA386 Committee papers, used in TA756 as well, and included in the model*." The EAG notes that cost and disutility calculations use the AE incidence arrays from FREEDOM which do not include AML. Please clarify how AML was included in the model.

Response: AML incidence is now included in the model in both the fedratinib and BAT arms, with the same incidence in both arms. The incidence was retrieved from TA386, in which 4 of 73 patients had transformation to AML. This change does not materially affect the ICER.

Technical model queries

B38. Please respond to the following queries:

a) Model, 'Drug Costs' sheet, N173:N188: Please explain why relative dose intensities for the treatments in the BAT arm were not included in the calculations for pack duration.

b) Model, 'Drug Costs' sheet, rows 149 and 174: Please explain why busulfan was included in the oral treatments when the unit cost (D149:L149) appear to

relate to a solution for infusion rather than an oral tablet. Amend the sheet if necessary.

c) VBA, module ‘MODEL__FUNCTIONS’ line 582: Please clarify why last year was rounded down from (f_end -1) instead of (f_end).

d) VBA, module ‘MODEL__FUNCTIONS’ line 653: Please clarify why drug costs were incurred at the end of the interval (Start_Time + Discount_Looper * Recur_Interval) instead of the start (Start_Time + (Discount_Looper-1) * Recur_Interval)

e) VBA, module ‘MODEL_RUN_5_OUTCOMES’ line 205, 257, 324 and 360: Please clarify why only four different dose options for ruxolitinib were considered for applying the PAS discount instead of all the dose options enlisted in the Excel array ‘array_cost_acq_rux’

f) VBA, module ‘MODEL_RUN_5_OUTCOMES’ line 373 and 435: Please clarify why supportive care costs were discounted from the model start (the 7th argument of the function) instead of the time after fedratinib and BAT discontinuation.

Response:

a) For ruxolitinib, due to its dose derivation, RDI is already accounted for in the model. A 100% RDI was assumed for the other drugs.

b) The sheet has been amended to reflect the tablet form of busulfan. The cost, pack size, and strength have been amended accordingly. This has no impact on the results, as busulfan was not given to patients in the model base case.

c) This is done because function Func_Age_Utility_Adjustment is assessing the length of time a patient is in a state via 0 indexing instead of the usual 1 indexing (e.g., if f_Start = 0.4 and f_End = 7.3: First_Year = 1 [rounded up], and Last_Year = 6 [rounded down]). (Not 2 to 7 if indexed based off 1 instead of 0). The function works by calculating the QALY multipliers over any full years (i.e., in the example above years 1 to [and including] 6), then adds the

remainders, which sit outside the whole years (i.e., 0.6 at the start and 0.3 at the end).

d) Thank you for highlighting this programming error. It has been corrected as suggested. This has a similar marginal impact on both treatments, with total discounted costs increasing from [redacted] to [redacted] for BAT and from [redacted] to [redacted] for fedratinib. The cost-savings associated with fedratinib are now [redacted] (previously [redacted]).

e) Thank you for highlighting this programming error. It has been corrected from 4 to 9 to account for all the ruxolitinib treatments type. It only affects results when a PAS is implemented for ruxolitinib and therefore has no impact on the results shared.

f) The supportive care costs were discounted from the model start, as some patients can get to the supportive care start as soon as 1 cycle after the model started.

Section C: Textual clarification and additional points

C1. The text above CS Table 55 gives numbers that differ by 0.001 versus those in CS Table 55. Please confirm if the data in the table are correct and the data in the text are typos.

Response: Thank you for identifying this. Data in the table are correct. The numbers in the text are taken directly from the statistical utility analysis. The numbers in Table 55 are taken from the implementation of this in the economic model; the 2 differ slightly due to rounding in the economic model inputs.

C2. CS Table 97 in Appendix J: Why are there zero acquisition costs in the ‘JAKi state’ for the intervention arm, with the majority of the costs falling in the ‘BAT state’? One would expect the majority of the acquisition costs to be in the ‘JAKi state’ with smaller costs in the BAT state for those non-responding or discontinuing fedratinib.

Are the intervention and comparator columns mislabelled? Comparison against CS Table 75 in Doc B suggests they are. Please confirm.

Response: Thank you for identifying this. Table 97 columns are mislabelled. BAT and fedratinib labels are inverted.

C3. Text on page 132 says the tornadoes are constructed using incremental net monetary benefits and a willingness to pay threshold (WTP) of £30,000 but they appear to present ICERs according to x axis of CS Figure 44. Please clarify.

Response: Thank you for identifying this. We can confirm that Figure 44 presents ICERs.

This is a pasting error, please see below the graph with the INMB:

C4. Please provide the exact settings changed from the base case for each scenario presented in CS Table 83. Please also identify which survival curve is being applied with reference to tables and figures in Appendix M. Please also clarify which quadrant the ICERs lie in for non-dominated scenarios in CS Table 83. It would be helpful if both incremental costs and incremental QALYs could be provided for all the scenarios presented in CS Table 83 so the EAG can validate these scenarios.

Response: Thank you for your request, in a few instances the incorrect values were reported. Please find below the scenarios with amended values. Details on the changes that are made for each scenario can be found in the Table beginning in cell F213 in sheet ‘Scenario Analysis’.

Scenario	Model settings
OS equal in fedratinib and BAT; TTD equal in fedratinib and BAT. Distributions assigned: ▪ FED OS: Gompertz ▪ FED TTD: log-logistic ▪ BAT OS: Gompertz BAT TTD: log-logistic	▪ Distributions assigned: ▪ FED OS non-responders: Gompertz ▪ FED OS responders: Gompertz ▪ FED TTD responders: log-logistic ▪ FED TTD non-responders: log-logistic ▪ BAT OS responders: Gompertz ▪ BAT OS non-responders: Gompertz ▪ BAT TTD responders: log-logistic ▪ BAT TTD non-responders: log-logistic
OS equal in fedratinib and BAT; TTD equal in fedratinib and BAT. Distributions assigned: ▪ FED OS: Weibull ▪ FED TTD: gen gamma ▪ BAT OS: Weibull BAT TTD: gen gamma	▪ Distributions assigned: ▪ FED OS responders: Weibull ▪ FED OS non-responders: Weibull ▪ FED TTD responders: gen gamma ▪ FED TTD non-responders: gen gamma ▪ BAT OS responders: Weibull ▪ BAT OS non-responders: Weibull ▪ BAT TTD responders: gen gamma ▪ BAT TTD non-responders: gen gamma
OS and TTD separated only by treatment. Distributions assigned: ▪ FED OS: Weibull ▪ FED TTD: exponential ▪ BAT OS: Weibull BAT TTD: exponential	Distributions assigned: ▪ FED OS responders – separated by treatment only: Weibull ▪ FED OS non-responders – separated by treatment only: Weibull ▪ FED TTD responders – separated by treatment only: exponential ▪ FED TTD non-responders – separated by treatment only: exponential ▪ BAT OS responders – separated by treatment only: Weibull ▪ BAT OS non-responders – separated by treatment only: Weibull ▪ BAT TTD responders – separated by treatment only: exponential ▪ BAT TTD non-responders – separated by treatment only: exponential

Scenario	Model settings
OS equal in fedratinib and BAT; separate TTD. ▪ FED OS: Weibull ▪ FED TTD: exponential ▪ BAT OS: Weibull BAT TTD: exponential	▪ FED OS responders – pooled Fed/BAT: Weibull ▪ FED OS non-responders – pooled Fed/BAT: Weibull ▪ FED TTD responders – separate by treatment only: exponential ▪ FED TTD non-responders – separate by treatment only: exponential ▪ BAT OS responders – pooled Fed/BAT: Weibull ▪ BAT OS non-responders – pooled Fed/BAT: Weibull ▪ BAT TTD responders – separate by treatment only: exponential ▪ BAT TTD non-responders – separate by treatment only: exponential
Equal OS and TTD for fedratinib and BAT. ▪ FED OS: Weibull ▪ FED TTD: log-logistic ▪ BAT OS: Weibull ▪ BAT TTs: log-logistic Does not include AE disutility. Does not include worsening utility on supportive care to both fedratinib and BAT.	▪ FED OS responder – pooled Fed/BAT: Weibull ▪ FED OS non-responder – pooled Fed/BAT: Weibull ▪ FED TTD responder – pooled Fed/BAT: log-logistic ▪ FED TTD non-responder – pooled Fed/BAT: log-logistic ▪ BAT OS responder – pooled Fed/BAT: Weibull ▪ BAT OS non-responder – pooled Fed/BAT: Weibull ▪ BAT TTD responder – pooled Fed/BAT: log-logistic ▪ BAT TTD non-responder – pooled Fed/BAT: log-logistic Include adverse event disutility? No Include worsening utility on supportive care to both the fedratinib and BAT arm? No

Scenario	Model settings
No crossover for BAT ▪ FED OS: Weibull ▪ BAT OS: log-logistic ▪ FED TTD: log-logistic ▪ BAT TTD: log-logistic	▪ FED OS responder – pooled Fed/BAT: Weibull ▪ FED OS non-responder – pooled Fed/BAT: Weibull ▪ FED TTD responder – pooled Fed/BAT: log-logistic ▪ FED TTD non-responder – pooled Fed/BAT: log-logistic ▪ BAT OS responder – no crossover: log-logistic ▪ BAT OS non-responder – no crossover: log-logistic ▪ BAT TTD responder – no crossover: log-logistic ▪ BAT TTD non-responder – no crossover: log-logistic
OS and TTD separated only by treatment. Distributions assigned: ▪ FED OS: log-normal ▪ FED TTD: log-normal ▪ BAT OS: Weibull ▪ BAT TTD: log-logistic	▪ FED OS responder – separated by treatment only log-normal ▪ FED OS non-responder – separated by treatment only log-normal ▪ FED TTD responder – separated by treatment only log-normal ▪ FED TTD non-responder – separated by treatment only log-normal ▪ BAT OS responder – separated by treatment only Weibull ▪ BAT OS nonresponder – separated by treatment only Weibull ▪ BAT TTD responder – separated by treatment only log-logistic ▪ BAT TTD non-responder - separated by treatment only log-logistic
OS and TTD are split by treatment and response status. Distributions assigned: ▪ FED OS NR: log-normal ▪ FED OS R: log-normal ▪ FED TTD NR: log-logistic ▪ FED TTD R: gen gamma ▪ BAT OS NR: Weibull ▪ BAT OS R: no crossover: log-normal ▪ BAT TTD NR: exponential ▪ BAT TTD R: gen gamma	▪ FED OS responder –log-normal ▪ FED OS non-responder –log-normal ▪ FED TTD responder –log-logistic ▪ FED TTD nonresponder –gen gamma ▪ BAT OS responder –Weibull ▪ BAT OS nonresponder – no-cross over log-normal ▪ BAT TTD responder –exponential ▪ BAT TTD non-responder - gen gamma

Scenario	Model settings
OS and TTD are split by treatment and response status. Distributions assigned: ▪ FED OS NR: Weibull ▪ FED OS R: Weibull ▪ FED TTD NR: log-normal ▪ FED TTD R: log-normal ▪ BAT OS NR: log-normal ▪ BAT OS R: no crossover: log-normal ▪ BAT TTD NR: exponential ▪ BAT TTD R: gen gamma	▪ FED OS responder - log-normal ▪ FED OS non-responder – log-normal ▪ FED TTD responder –log-logistic ▪ FED TTD non-responder – separated by treatment only gen gamma ▪ BAT OS responder –Weibull ▪ BAT OS non-responder – no-cross over log-normal ▪ BAT TTD responder –exponential ▪ BAT TTD non-responder - gen gamma
Responder scenario 1: OS is split by treatment and response status. TTD remains pooled FED/BAT. Distributions assigned: ▪ FED OS NR: Weibull ▪ FED OS R: Weibull ▪ BAT OS NR: log-logistic ▪ BAT OS R (pooled FED/BAT): Weibull Suboptimal FED: 0%	▪ TTD pooled Fed/bat – settings as base case ▪ FED OS non-responder - Weibull ▪ FED OS responder – Weibull ▪ BAT OS non-responder –log-logistic ▪ BAT OS responder – pooled Fed/bat Weibull
Responder scenario 2: OS is split by treatment and response status. TTD remains pooled FED/BAT. Distributions assigned: ▪ FED OS NR: exponential ▪ FED OS R: exponential ▪ BAT OS NR: log-normal ▪ BAT OS R (pooled FED/BAT): exponential Suboptimal fed: 0%	▪ TTD pooled Fed/bat as in base case ▪ FED OS non-responder - exponential ▪ FED OS responder – exponential ▪ BAT OS non-responder –log-normal ▪ BAT OS responder – pooled Fed/bat exponential
Responder scenario 1: OS is split by treatment and response status. TTD remains pooled FED/BAT. Distributions assigned: ▪ FED OS NR: Weibull ▪ FED OS R: Weibull ▪ BAT OS NR: log-logistic ▪ BAT OS R (pooled FED/BAT): Weibull Suboptimal fed: 32.1%	▪ TTD pooled Fed/bat as in base case ▪ FED OS non-responder - Weibull ▪ FED OS responder – Weibull ▪ BAT OS non-responder –log-logistic ▪ BAT OS responder – pooled Fed/bat Weibull ▪ Manual input, fedratinib in BAT, after fedratinib (initial responders) 32.1% ▪ Fedratinib in BAT Live input 32.1%

Scenario	Model settings
Responder scenario 2: OS is split by treatment and response status. TTD remains pooled FED/BAT. Distributions assigned: ▪ FED OS NR: exponential ▪ FED OS R: exponential ▪ BAT OS NR: log-normal ▪ BAT OS R (pooled FED/BAT): exponential Suboptimal fed: 32.1%	▪ TTD pooled Fed/bat as in base case ▪ FED OS non-responder - exponential ▪ FED OS responder – exponential ▪ BAT OS non-responder –log-normal ▪ BAT OS responder – pooled Fed/bat exponential ▪ Manual input, fedratinib in BAT, after fedratinib (initial responders) 32.1% ▪ Fedratinib in BAT Live input 32.1%
Fedratinib in BAT after fedratinib treatment: 25%	▪ Manual input, fedratinib in BAT, after fedratinib (initial responders) 25%
Fedratinib in BAT after fedratinib treatment: 50%	▪ Manual input, fedratinib in BAT, after fedratinib (initial responders) 50%
Fedratinib in BAT after fedratinib treatment: 65%	▪ Manual input, fedratinib in BAT, after fedratinib (initial responders) 65%
Use of mean dose for ruxolitinib dosing in BAT	▪ Ruxolitinib cost based on distribution or mean dose: Mean dose ▪ Include “additional” wastage for ruxolitinib treatment? (based on TA386 assumptions): Yes

C5. The KM curves in the ‘KM Data’ sheet of the model for FREEDOM-2 (columns IA onwards) appear to record time in weeks but this does not correlate with the TTD or OS data presented in the CS. For example, CS Figure 40 has [redacted] TTD at around 12 months, whereas this occurs at around 12 weeks according to the data in the KM sheet (median duration of exposure in CS Table 26 is 43 weeks for fedratinib suggesting a median TTD that is closer to 12 months than 12 weeks). Please confirm if the time within the KM curves in the model ‘KM Data’ sheet is actually in months rather than weeks.

Response: The time in the ‘KM data’ sheet is in weeks and is then converted to years for graph purposes. In the model, ‘TTD data’ sheet, cell AO 60, the graph shows that the median KM is at approximately 52 weeks (i.e., 1 year).

C6. The EAG notes that all of the figures in the ‘TTD Data’ sheet are pasted in as images. This means that the EAG is unable to see how they have been generated and whether the KM data corresponds to that provided in the ‘KM Data’ sheet. Please either provide the workbook used to generate these plots or make these plots

‘live’ within the model so that they are generated by data provided within the Excel file.

Response: We have included a new sheet ‘Example_OS_calculations’ which shows how the time to event parameters are calculated. The KM data used are provided in the ‘KM Data’ sheet.

C7. Please clarify if the values given for median haemoglobin at baseline are in g/L and not g/dL as stated in CS Table 6 (i.e., they should be 9.3g/dL and 9.4g/dL respectively for each arm). These values would be more in keeping with the plot of haemoglobin over time shown in CSR Figure 8.7.1-1.

Response: Thanks for pointing this out. This is a typo; it should read as 9.3 g/dL and 9.4 g/dL.

NICE National Institute for Health and Care Excellence

Cancer Drugs Fund Review

Fedratinib for treating disease-related splenomegaly or symptoms in myelofibrosis (Review of TA756) [ID5115]

Guidance review following a period of managed access - Patient organisation submission

Thank you for agreeing to give us your organisation's views on this treatment following a period of managed access. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

PLEASE NOTE: You do not have to answer every question. Your organisations involvement in the managed access agreement for this treatment is likely to determine which questions you can answer.

To help you give your views, please use this questionnaire with **NICE's guide for patient organisations "completing an organisation submission following a period of Managed Access for Technology Appraisals or Highly Specialised Technologies".** Please contact pip@nice.org.uk if you have not received a copy with your invitation to participate.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 20 pages.

NICE National Institute for Health and Care Excellence

This form has 8 sections

NICE National Institute for Health and Care Excellence

Section 1. About you

Table 1 Name, job, organisation

1. Your name	[redacted]
2. Name of organisation	MPN Voice & Leukaemia Care
3. Job title or position	[redacted]
4a. Provide a brief description of the organisation. How many members does it have?	MPN Voice is the patient support organisation for people with Myeloproliferative Neoplasms (MPNs) in the UK. MPN Voice's mission is to provide clear and accurate information and emotional support to everyone who has been diagnosed with a myeloproliferative neoplasm and their families/friends. MPN Voice has members across the UK and in many other countries throughout the world. MPN Voice offers a website (http://www.mpnvoice.org.uk), patients' forums around the UK during the year, and a Peer Support programme to allow people with MPNs to contact others in similar circumstances. MPN Voice also has an online forum at HealthUnlocked which is a supportive and informative online forum where patients and carers can ask questions about anything related to MPNs and get replies from people who really understand the challenges of living with an MPN. In addition, MPN Voice produces information leaflets and a newsletter for people with MPNs so that patients are better informed and have more confidence dealing with the management of their condition. MPN Voice also raises money to fund research towards a cure and advocacy for patients. MPN Voice's work is primarily funded by donations from the public, through a wide range of fundraising activities. MPN Voice also accepts financial support from pharmaceutical companies for specific activities (see below)

	Leukaemia Care is the UK's leading leukaemia charity. For over 50 years, we have been dedicated to ensuring that everyone affected by leukaemia, MDS or MPNs receives the best possible diagnosis, information, advice, treatment and support. Approximately 80% of our income comes from fundraising activities – such as legacies, community events, marathons etc. Leukaemia Care also receives funding from a wide range of pharmaceutical companies, but in total those funds are less than 20% of our annual income. Leukaemia Care has undertaken a voluntary commitment to adhere to specific policies that regulate our involvement with the pharmaceutical industry set out in our code of practice here: https://media.leukaemiacare.org.uk/wp-content/uploads/Leukaemia-CARE-Code-of-Practice-pdf.
4b. Has the organisation received any funding from the company/companies of the treatment and/or comparator products in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list which was provided to you when the appraisal started] **If so, please state the name of company, amount, and purpose of funding.**	Leukaemia Care Bristol-Myers Squibb: £30,000 - £15k core funding and £15k on behalf of the Blood Cancer Alliance, of which Leukaemia Care is a member. MPN Voice GlaxoSmithKline: £30,000 for core support services & £685 for honoraria and review of PIL Novartis: £14,680 support for Ireland patient forum, £3,000 consultancy for MPN 10 artwork campaign, £60,000 support for patient reported outcomes and wearables study linked to the My MPN Voice app.
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No, for both organisations

5. How did you gather information about the experiences of patients and carers to include in your submission?	Data supporting this submission has been gathered from a range of sources: MPN Voice is a founding member of MPN Advocates Network (MPNAN), a global coalition of MPN Patient groups. In 2019 MPNAN began the largest survey of MPN patient needs to date, with over 1800 responses at the time of writing. Over 300 responses have been received from myelofibrosis patients. Evidence has also been taken from two MPN Landmark studies, the original US-based one in 2016 and a subsequent international study. The 2016 study had 816 respondents, of which 207 were Myelofibrosis patients. The international study had 174 responses from myelofibrosis patients, 45 from the UK, and provides information on patient reported quality of life and productivity. (Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5569657/) This submission is also informed by a patient experience survey of 34 adults diagnosed with myelofibrosis, carried out by Leukaemia Care in 2016. This was part of a wider survey of over 2500 blood cancer patients. Further, in 2023 MPN Voice conducted a targeted survey of MF patients and their family and carers in the UK, to gain information about their real-life experience of living with MF and its symptoms, plus the impact, both positive and negative, of the drugs with which they have been treated. Responses were received from 197 MF patients and 57 family and carers. Lastly, we have carried out telephone interviews in early 2024, with five MF patients already treated with Fedratinib (including several taking it in conjunction with interferon) to understand more about their experience of this drug and any other drugs with which they may have previously been treated.

Section 2 Living with the condition and current treatment

Table 2 What it's like for patients, carers and families to live with the condition and current NHS treatment

6. What is it like to live with the condition? Consider the experience of living with the condition and the impact on daily life (physical and emotional health, ability to work, adaptations to your home, financial impact, relationships, and social life). For children, consider their ability to go to school, develop emotionally, form friendships and participate in school and social life. Is there any impact on their siblings?	Myelofibrosis (MF) is a rare form of blood cancer, known as a myeloproliferative neoplasm (MPN), that causes the overproduction of fibroblasts in the bone marrow. There are fewer than 1-2 people per 100,000 diagnosed every year in the UK. Most patients will be over the age of 50 years old at diagnosis, with the average age in the Landmark study being 59.6 years old. There are two types of myelofibrosis, primary and secondary. In primary MF the disorder has arisen by itself and secondary MF is a progression from another MPN. Around 50-60% of MF patients will have a mutation in the JAK2 protein. The international MPN Landmark study performed a systematic analysis of the burden of MPN illnesses. Quoting from the peer-reviewed report of the study, "*MPNs are associated with a substantial disease burden, often leading to a reduced quality of life (QOL) for many patients. Symptoms may include fatigue, pruritus, night sweats, microvascular symptoms, splenomegaly, and splenomegaly associated symptoms (e.g., abdominal pain, early satiety), with fatigue being one of the most severe symptoms. Among patients with MF, PV, or ET, patients with MF generally have the highest symptom burden and the lowest QOL*." MF patients reported to the 2016 Landmark researchers a range of symptoms. The following are illustrations of the numbers of patients for whom the symptoms have a significant impact: • Fatigue 80% of patients • Depression or sad mood 75% • Abdominal discomfort 53% • Night sweats 51% Respondents to the MPN Voice 2023 survey of MF patients reported the following symptoms most frequently: • Fatigue 91% of patients • Weakness 45% • Bruising or bleeding 40% • Abdominal discomfort 34%

	• Bone pain 34% • Excessive sweating 30% Apart from the actual symptoms, MF affects many other aspects of patients' lives. The MF patients in the UK who responded to the MPNAN survey scored 4.2/10 in terms of financial impact (0 being the most significant impact). Over 30% of these patients reported significant financial difficulties. 66% of patients responding to the latest survey reported that MF impacted their ability to carry out everyday tasks and activities. 65% reported that MF impacted their ability to work, with the same percentage reporting a significant impact on their own social life and that of their carers. One patient who we spoke to in January 2024 told us about the significant symptoms that MF caused for him – he suffered badly from fatigue, severe itching of his skin and night sweats, which prevented him from sleeping. These symptoms in turn meant him giving up full-time work and had a significant impact on his social and family life, becoming dependent on others for everyday tasks that he used to do for them. Another patient had been able to retire in his mid 50's but was diagnosed with MF within 12 months of that and now found himself facing the prospect of living with the heavy symptom burden of MF rather than enjoying the active retirement he had been hoping for. A 32-year-old patient reported that her fatigue and lack of sleep became so debilitating that initially she had to sleep during rest breaks at work and was then signed off work on medical grounds, while still needing to find the energy to care for her two young children. Some of the comments from patients responding to the 2023 MPN Voice survey included: 'I get tired easily and have had to retire on ill health grounds from working as GP due to fatigue/struggling cognitively.' 'I become totally out of energy in 10 seconds, I just need a rest there and then. I am really feeling tired just by thinking of a task I need to do'

	'My husband has had to take over shopping and cooking. Not walking too far, have applied for a blue badge' 'Extreme fatigue and bone pain make it impossible on some days to stand and cook, walk dog, play with kids, socialise' 'I am no longer able to work. The fatigue has not changed only gets worse. Infections are pretty frequent, and transfusions are now a big part of maintaining haemoglobin. I need shopping, cooking, cleaning and driving all done for me' 'I have not been able to work for years due to level of fatigue and or chronic skeletal pain' 'Was working full time in demanding job but have taken early retirement due to constant fatigue and recurring infections' 'I have a shorter active day because of fatigue and also, I miss sleep due to night sweats. Also, I have inertia and loss of concentration some days which makes it difficult to do things' The disease significantly impacts the economic productivity of patients and their carers. The 2016 Landmark survey reported that 59% of MF patients had reduced work hours owing to the disease.
7. What do carers experience when caring for someone with the condition?	The significant impact of the disease is also felt by the people who care for MF patients. This impact is felt in a variety of ways, from the psychological and emotional burden of caring for someone with an incurable, debilitating disease, to the practical and financial effect. On average respondents to the MPNAN survey who specifically identified as carers of MF patients scored 6.7/10 for the impact on their ability to work (10 meaning they couldn't work at all), and over 30% reported that they were unable to work at all because of their role as carers. From the latest MPN Voice survey, 58% of carers reported having to support the patient with everyday tasks and activities, with a significant impact on their own day to day life and on their relationship with the

	patient. 32% of carers reported that providing this support had significantly impacted their own ability to work.
8. What do patients and carers think of current treatments and care available on the NHS Please state how they help and what the limitations are.	Following diagnosis, some patients who aren't experiencing symptoms will be put on 'Watch and Wait' where the MF is monitored over time. In the Leukaemia Care (LC) survey, 29% of patients were placed on Watch and Wait and this caused some level of concern or worry for many patients. Overall, 62% of MF patients felt to some extent more depressed or anxious following diagnosis, including those who had started treatment or were still on Watch and Wait, demonstrating the significant emotional impact that a diagnosis has on the patient. Other MF patients will be given treatments to manage MF and the side effects, as the only curative option is stem cell transplant. With this being an intensive treatment option, it is not often advised. Just 9% of patients in the Leukaemia Care survey had received a stem cell transplant. LC asked about the side effects of their current treatments, the majority of patients experienced side effects (94%) with the most common being: fatigue (68%), sleeping problems (41%), bruising (41%), sore mouth (38%), anaemia (35%), loss of concentration/memory (32%), and breathing difficulties (32%). The side effects had an impact on 82% of patients (54% small impact, 25% large impact, 4% intolerable). Comments from patients receiving the current treatments generally underline their concerns about both side-effects and the limited effectiveness of these drugs, especially over time. They hope that other treatments may become available that offer longer-term efficacy and less debilitating side-effects. LC also gained anonymous evidence from three patients about their treatment with ruxolitinib (the primary targeted treatment currently available to UK patients). The degree to which the treatment impacted on their symptoms was very different, with one patient saying symptoms had got worse, and the others stating symptoms had partially or significantly improved. One patient stated that they failed to respond to ruxolitinib after 2-3 years and their spleen enlarged. This was their most recent treatment for MF, demonstrating the lack of options for patients. One patient we spoke to in 2024 had originally been treated with hydroxycarbamide, which gave little relief from splenomegaly and other symptoms and he was not considered a suitable candidate for ruxolitinib due to other previous cancers, hence the decision to try fedratinib.

	Another 2024 patient had initially seen some positive response from ruxolitinib but that waned over time and an alternative targeted therapy was needed.
9. Considering all treatments available to patients are there any unmet needs for patients with this condition? If yes please state what these are	Most therapies for MF focus on controlling the symptoms of the disease and these, particularly non-targeted therapies such as hydroxycarbamide and interferon, are not effective for all MF patients; many patients also do not tolerate their side effects well. Ruxolitinib treatment is effective for some patients, but response is frequently inadequate. Furthermore, the median duration of response to ruxolitinib is 3 years and we are seeing increasing numbers of patients with progressive disease after previous response to ruxolitinib. To quote from the Dec 2019 paper *Beyond Ruxolitinib: Fedratinib and Other Emergent Treatment Options for Myelofibrosis*, "…patients who discontinue ruxolitinib have dismal outcomes, making this situation an area of significant unmet need" This patient group (those who need to discontinue ruxolitinib treatment) represents an area of major unmet medical need as currently there are no approved targeted therapies for this patient group in the UK. Whilst we recognise that approval of momelotinib as an alternative targeted therapy is expected soon, we believe it is important that clinicians have access to a wider range of potential targeted treatments for MF patients, to allow the use of those that best match each patient's needs in terms of symptoms and prognosis. The lack of other effective treatments for patients who are unresponsive to or intolerant of ruxolitinib and other drugs is a source of concern for many of the patients who responded to the 2023 survey. Even those who respond initially to other treatments can be aware of the potential for them to stop working, meaning that anxiety has a further impact on their quality of life, especially as they see the efficacy of ruxolitinib beginning to wane, or their side effects getting worse. Comments in this area included: 'My concern is that for 50 percent of patients ruxolitinib stops working after two to three years - there isn't yet a viable follow-on medication.' 'I'm only 53 and worry that the Jakafi will lose effectiveness over time. I feel an additional treatment option is important' 'Anxiety of what happens when medication is no longer effective'

	'I have been taking 20mg of Rux for 6 years now (2 x 10mg) a day. This was increased to 25mg a day because my spleen has started growing back. The increase in dosage has helped reduce it but I worry a lot about it ultimately losing its effect' 'After 18 months on Ruxolitinib 5mg x 2. Symptoms have got worse, weight loss & loss of appetite, bruises & night sweats' 'Although the medication (ruxolitinib) has had a positive effect on my blood results, it has had a negative effect on my energy levels, fatigue being my biggest concern'

Section 3 Experience during the managed access agreement (MAA)

Table 3 Experience, advantages and disadvantages during the MAA

10. What are patients' and carers' experience of accessing and having the treatment? • Please refer to the MAA re-evaluation patient submission guide	All of the patients that we spoke to recently (both those being treated with fedratinib only, under the managed access agreement and those being treated concurrently with interferon) were pleased to have been offered the opportunity of treatment with fedratinib, either where previous treatments were no longer effective or, in one case, where the patient's previous medical history made them unsuitable for treatment with ruxolitinib. All of the patients were tolerating fedratinib well, despite some initial side effects after the first doses (see below) and were keen to continue treatment with it.
11. What do patients and carers think are the advantages of the treatment?	When compared to any previous treatments, the patients interviewed in early 2024 reported that fedratinib provided better control of their MF symptoms, such as fatigue, night sweats, bone pain and severe itching. Three patients had suffered badly with splenomegaly, which had reduced significantly once being treated with fedratinib. Quotes from these recent patient interviews included:

Please refer to the MAA re-evaluation patient submission guide	'After ruxolitinib stopped working I thought I'd reached the end, I scratched my skin till it bled and had to use a frame for walking. Fedratinib has been a wonder drug for me – I can do a lot more than I did before and only experience the fatigue maybe one or two days a month.' 'The size of my spleen made it difficult for me to walk, eat and sleep due to the pain. This treatment (fedratinib & interferon) has helped me get my life back.' 'Fedratinib has been a game changer for me – it's reduced all my symptoms and has made me more mobile and independent.' 'It (fedratinib & interferon) has been amazing – I was shocked how quickly I felt normal again and within four months my spleen had reduced from over 20cm to normal size. Fedratinib is my new favourite drug and I'd have been keen to stay on it if I hadn't recently been approved for a stem cell transplant'
12. What do patients or carers think are the disadvantages of the treatment? Please refer to the MAA re-evaluation patient submission guide	Most of the patients interviewed reported some nausea after taking the initial dose or doses of fedratinib but this was reduced by taking it with food and resolved completely within a few weeks. One patient experienced extreme fatigue at the start of treatment. The dosage was therefore reduced, which has resolved that side effect for her, while still providing very good relief from MF symptoms. Some patients found more frequent clinic visits inconvenient, but this was deemed acceptable in view of their overall improved quality of life.
13. What place do you think this treatment has in future NHS treatment and care for the condition? Consider how this treatment has impacted patients and how it fits alongside other treatments and care pathway.	MF is a complex, progressive illness and patients often suffer from other related complications that make treatment decisions complicated. Existing treatments all have their own side effect profiles and therefore additional therapies are needed to help specialists optimise their therapeutic approach. In this context, fedratinib appears to offer another effective targeted treatment option for those MF patients who are ineligible for stem cell transplant and for whom other treatments are either ineffective or unsuitable.

Section 4 Patients views on assessments used during the MAA

Table 4 Measurements, tests and assessments

14. Results from tests and assessments are used to help reduce uncertainty about the effectiveness of treatment. **How well do you think these tests and assessments worked in measuring the effectiveness of the treatment?**	Unable to comment
15. Were there any tests or assessments that were difficult or unhelpful from a patient's or carer's perspective?	Unable to comment
16. Do patients and carers consider that their experiences (clinical, physical, emotional and psychological) were captured adequately in the MAA tests and assessments? If not please explain what was missing.	Unable to comment

17. What outcomes do you think have not been assessed or captured in the MAA data? Please tell us why	Unable to comment

Section 5 Patient population

Table 5 Groups who may benefit and those who declined treatment

18. Are there any groups of patients who might benefit more or less from the treatment than others? If so, please describe them and explain why.	All patients are likely to benefit from this treatment, due to very limited treatment options currently available for MF patients. This will further benefit patients who are unable to tolerate other existing treatments, or whose MF does not respond to them, and who are ineligible for stem cell transplant.
19. Were there people who met the MAA eligibility criteria who decided not to start treatment? Please state if known the proportion of eligible patients who did not start the treatment and any reasons for this.	Unable to comment

Section 6 Equality

20. Are there any potential equality issues that that should be taken into account when considering this condition and the treatment? See NICE's equality scheme for more details.

Section 7 Other issues

21. Are there any other issues that you would like the committee to consider?

Not at this time.

Section 8 Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Myelofibrosis is a debilitating chronic condition that has a major impact on patients' quality of life, with significant negative social and economic impacts on patients and their carers
- The only cure for MF is a stem cell transplant but this is not an option for the majority of patients
- Non-targeted treatments such as hydroxycarbamide and interferon are of limited effectiveness in MF and there is therefore an unmet need for a range of targeted treatment options
- Even where there is an initial response to a targeted therapy such as ruxolitinib, this often wanes over time and the prognosis for these refractory patients is currently very poor
- Based on the evidence collected from patients, we believe that fedratinib is an important alternative targeted treatment option for myelofibrosis

Thank you for your time.

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NDRS
NATIONAL DISEASE REGISTRATION SERVICE

NHS England

Fedratinib for treating disease-related splenomegaly or symptoms in myelofibrosis – data review

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About the NDRS

The National Disease Registration Service (NDRS) is part of NHS England. Its purpose is to collect, collate and analyse data on patients with cancer, congenital anomalies, and rare diseases. It provides robust surveillance to monitor and detect changes in health and disease in the population. NDRS is a vital resource that helps researchers, healthcare professionals and policy makers make decisions about NHS services and the treatments people receive.

The NDRS includes:

- the National Cancer Registration and Analysis Service (NCRAS) and
- the National Congenital Anomaly and Rare Disease Registration Service (NCARDRS)

Healthcare professionals, researchers and policy makers use data to better understand population health and disease. The data is provided by patients and collected by the NHS as part of their care and support. The NDRS uses the data to help:

- understand cancer, rare diseases, and congenital anomalies
- improve diagnosis
- plan NHS services
- improve treatment
- evaluate policy
- improve genetic counselling

NDRS
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Contents

1. Executive summary

Introduction

The National Institute for Health and Care Excellence (NICE) appraised the clinical and cost effectiveness of fedratinib for the treatment of disease-related splenomegaly or symptoms in myelofibrosis. The appraisal committee highlighted clinical uncertainty around estimates of overall survival (OS) in the evidence submission. As a result, they recommended the commissioning of fedratinib through the Cancer Drugs Fund (CDF) to allow a period of managed access, supported by additional data collection to answer the clinical uncertainty.

NHS England have evaluated the real-world treatment effectiveness of fedratinib in the CDF population, during the managed access period. This report presents the results of the use of fedratinib in clinical practice in England, using the routinely collected Systemic Anti-Cancer Therapy (SACT) dataset.

This report, and the data presented, demonstrate the potential within the English health system to collect real-world data to inform decision-making about patient access to cancer treatments via the CDF. The opportunity to collect real-world data enables patients to access promising new treatments much earlier than might otherwise be the case, whilst further evidence is collected to address clinical uncertainty.

The collection and follow up of real-world SACT data for patients treated through the CDF in England has resulted in analysis being carried out on 89% of patients and 89% of patient outcomes reported in the SACT dataset. NHS England are committed to providing world first, high-quality real-world data on CDF cancer treatments to be appraised alongside the outcome data from the relevant clinical trials.

Methods

The NHS England Blueteq® system was used to provide a reference list of all patients with an application for fedratinib for the treatment of disease-related splenomegaly or symptoms in myelofibrosis in the CDF. Patient NHS numbers were used to link Blueteq applications to NDRS' routinely collected SACT data to provide SACT treatment history.

Between 17 November 2021 and 31 October 2022, 75 applications for fedratinib were identified in the Blueteq system. Following appropriate exclusions (see Figures 1 and 2), 54 unique patients who received treatment were included in these analyses. All patients were traced to obtain their vital status using the personal demographics service (PDS)[1].

Results

54/61 (89%) unique patients with CDF applications were reported in the SACT dataset and were included in the final cohort.

Median treatment duration was 5.7 months [95% CI: 3.9, 9.7] (173 days). 50% of patients were still receiving treatment at 6 months [95% CI: 34%, 64%] and 29% of patients were still receiving treatment at 12 months [95% CI: 13%, 48%].

At data cut off, 50% (N=27) of patients were identified as no longer being on treatment. Of these 27 patients:

- 26% (N=7) of patients stopped treatment due to acute toxicity
- 26% (N=7) of patients died on treatment
- 22% (N=6) of patients stopped treatment due to disease progression
- 19% (N=5) of patients died not on treatment
- 7% (N=2) of patients chose to end their treatment

The median OS was not reached. OS at 6 months was 74% [95% CI: 59%, 83%] and 12 months OS was 57% [95% CI: 40%, 71%].

A treatment duration and OS sensitivity analysis was conducted for a cohort with at least 6 months' data follow-up in the SACT dataset. Results were consistent with the full analysis cohort.

Conclusion

This report analysed SACT real-world data for patients treated with fedratinib for the treatment of disease-related splenomegaly or symptoms in myelofibrosis in the CDF. It evaluated treatment duration, OS and treatment outcomes for all patients treated with fedratinib for this indication.

Introduction

Fedratinib is recommended for use within the Cancer Drugs Fund as an option for treating disease-related splenomegaly or symptoms of primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis in adults. It is recommended, only if:

- they have previously had ruxolitinib and
- the conditions in the managed access agreement for fedratinib are followed[2].

2. Background to this report

Using routinely collected data to support effective patient care

High quality and timely cancer data underpin NHS England's ambitions of monitoring cancer care and outcomes across the patient pathway. NHS England produces routine outcome reports on patients receiving treatments funded through the Cancer Drugs Fund (CDF) during a period of managed access using Systemic Anti-Cancer Therapy (SACT) data collected by the National Disease Registration Service (NDRS).

The CDF is a source of funding for cancer drugs in England[3]. From 29 July 2016 NHS England implemented a new approach to the appraisal of drugs funded by the CDF. The new CDF operates as a managed access scheme that provides patients with earlier access to new and promising treatments where there is uncertainty as to their clinical effectiveness. During this period of managed access, ongoing data collection is used to answer the clinical uncertainties raised by the NICE committee and inform drug reappraisal at the end of the CDF funding period[4].

NHS England analyse data derived from patient-level information collected in the NHS, as part of the care and support of cancer patients. The data is collated, maintained, quality-assured and analysed by the NDRS.

NICE Appraisal Committee review of fedratinib for treating disease-related splenomegaly or symptoms in myelofibrosis [TA756]

The NICE Appraisal Committee reviewed the clinical and cost effectiveness of fedratinib (Bristol Myers Squibb Pharmaceuticals Ltd) for the treatment of disease-related splenomegaly or symptoms in myelofibrosis [TA756] and published guidance for this indication in December 2021[5].

Due to the clinical uncertainties identified by the committee and outlined below, the committee recommended the commissioning of fedratinib for the treatment of disease-related splenomegaly or symptoms in myelofibrosis through the CDF for a period of 14 months, from November 2021 to January 2023. The drug will be funded through the CDF until NICE publish their final guidance.

During the CDF funding period, results from an ongoing clinical trial (FREEDOM 2[6]) evaluating fedratinib in the licensed indication are likely to answer the main clinical uncertainties raised by the NICE committee. Data collected from the FREEDOM 2 clinical trial is the primary source of data collection.

Analysis of the SACT dataset provides information on real-world treatment patterns and outcomes for fedratinib for the treatment of disease-related splenomegaly or symptoms in myelofibrosis in England, during the CDF funding period. This acts as a secondary source of information alongside the results of the FREEDOM 2 clinical trial[6].

The committee identified the key areas of uncertainty below for re-appraisal at the end of the CDF data collection;

- whether fedratinib extends overall survival compared to best available therapy
- overall survival for those on best available therapy

NHS England have calculated overall survival, other uncertainties listed above will be included in the FREEDOM 2 clinical trial results.

Treatment duration was not an area of clinical uncertainty but has been included in this report.

Approach

Upon entry to the CDF, representatives from NHS England, NICE and the company (Bristol Myers Squibb Pharmaceuticals Ltd) formed a working group to agree the Data Collection Agreement (DCA)[6]. The DCA set out the real-world data to be collected and analysed to support the NICE re-appraisal of fedratinib. It also detailed the eligibility criteria for patient access to fedratinib through the CDF, and CDF entry and exit dates.

This report includes patients with approved CDF applications for fedratinib, approved through Blueteq® and followed up in the SACT dataset collected by NDRS in NHS England.

3.Methods

CDF applications – identification of the cohort of interest

NHS England collects applications for CDF treatments through their online prior approval system (Blueteq®). The Blueteq application form captures essential baseline demographic and clinical characteristics of patients needed for CDF evaluation purposes. Where appropriate, Blueteq data are included in this report.

Consultants must complete a Blueteq application form for every patient receiving a CDF funded treatment. As part of the application form, consultants must confirm that a patient satisfies all clinical eligibility criteria to commence treatment. NDRS has access to the Blueteq database and key data items such as NHS number, primary diagnosis and drug information of all patients with an approved CDF application (which therefore met the treatment eligibility criteria).

The lawfulness of this processing is covered under Article 6(1)(e) of the United Kingdom (UK) General Data Protection Regulations (GDPR) (processing is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller). NHS England, through the National Disease Registration Service (NDRS), does have statutory authority to process confidential patient information (without prior patient consent) afforded through the National Disease Registries (NDRS) Directions 2021 issued to it by the Secretary of State for Health and Social Care, and has issued the NDRS Data Provision Notice under section 259 of the Health and Social Care Act 2012 regarding collection of the Blueteq data from NHS England.

NDRS in NHS England collates data on all SACT prescribed drugs by NHS organisations in England, irrespective of the funding mechanism. The Blueteq extract is therefore essential to identify the cohort of patients whose treatment was funded by the CDF.

Fedratinib clinical treatment criteria

- application is being made by, and the first cycle of systemic anti-cancer therapy with fedratinib will be prescribed by, a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy
- patient is an adult and has a diagnosis of primary myelofibrosis (also known as chronic idiopathic myelofibrosis) or post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis
- patient's myelofibrosis has a risk category that is either intermediate-2 or high risk
- patient has symptomatic disease-related splenomegaly and/or constitutional symptoms of myelofibrosis
- patient has been previously treated with ruxolitinib
- patient has an ECOG performance status (PS) of 0 or 1 or 2
- patients must have thiamine (vitamin B1) levels tested both before and during fedratinib therapy and that thiamine deficiency must be corrected before treatment starts and during fedratinib therapy
- in terms of active systemic therapy fedratinib is being given as monotherapy
- patient has not previously received fedratinib unless the patient has received fedratinib via a company early access scheme and the patient meets all the other criteria listed here
- fedratinib is to be continued until loss of clinical benefit or unacceptable toxicity or patient choice to stop treatment
- clinician is aware fedratinib has clinically important interactions with drugs which affect the CYP3A4, CYP2C19 and CYP2D6 enzyme systems
- a formal medical review as to how fedratinib is being tolerated and whether treatment with fedratinib should continue or not will be scheduled to occur at least by the start of the third 4-weekly cycle of treatment
- when a treatment break of more than 6 weeks beyond the expected 4-weekly cycle length is needed, a treatment break approval form will need to be completed to restart treatment, including indicating as appropriate if the patient had an extended break because of COVID-19
- fedratinib is to be otherwise used as set out in its Summary of Product Characteristics

CDF applications - de-duplication criteria

Before conducting any analysis on CDF treatments, the Blueteq data is examined to identify duplicate applications. The following de-duplication rules are applied:

1. If two trusts apply for fedratinib for the treatment of disease-related splenomegaly or symptoms in myelofibrosis for the same patient (identified using the patient's NHS number), and both applications have the same approval date, then the record where the CDF trust (the trust applying for CDF treatment) matches the SACT treating trust is selected.

2. If two trusts apply for fedratinib for the treatment of disease-related splenomegaly or symptoms in myelofibrosis for the same patient, and the application dates are different, then

the record where the approval date in the CDF is closest to the regimen start date in SACT is selected, even if the CDF trust did not match the SACT treating trust.

3. If two applications are submitted for fedratinib for the treatment of disease-related splenomegaly or symptoms in myelofibrosis and the patient has no regimen start date in SACT capturing when the specific drug was delivered, then the earliest application in the CDF is selected.

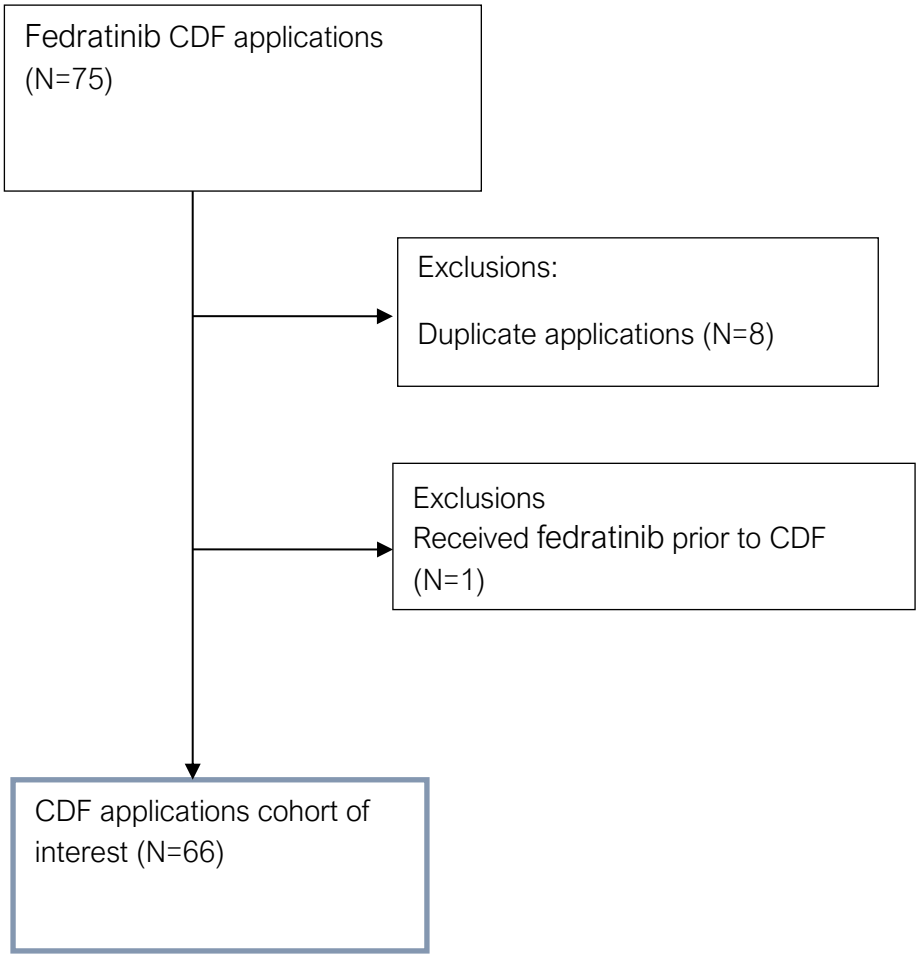
Initial CDF cohorts

The analysis cohort is limited to the date fedratinib entered the CDF for this indication, onwards. Any treatments delivered before the CDF entry date are excluded as they are likely to be patients receiving treatment via an Early Access to Medicines Scheme (EAMS) or a compassionate access scheme run by the company. These schemes may have different eligibility criteria compared to the clinical treatment criteria detailed in the CDF managed access agreement for this indication.

The CDF applications included in these analyses are from 17 November 2021 to 31 October 2022. A snapshot of SACT data was taken on 4 February 2023 and made available for analysis on 13 February 2023 and includes SACT activity up to 31 October 2022. Tracing the patients' vital status was carried out on 13 February 2023 using the Personal Demographics Service (PDS)[1].

There were 75 applications for CDF funding for fedratinib for the treatment of disease-related splenomegaly or symptoms in myelofibrosis between 17 November 2021 and 31 October 2022 in the NHS England Blueteq database. Following de-duplication this relates to 67 unique patients. One patient was excluded as they received fedratinib prior to the drug being available through the CDF.

Figure 1: Derivation of the cohort of interest from all CDF (Blueteq) applications made for fedratinib for the treatment of disease-related splenomegaly or symptoms in myelofibrosis between 17 November 2021 and 31 October 2022.



Linking CDF cohort to SACT

NHS numbers were used to link SACT records to CDF applications for fedratinib in the Blueteq system. Information on treatments in SACT were examined to ensure the correct SACT treatment records were matched to the CDF application; this includes information on treatment dates (regimen, cycle and administration dates) and primary diagnosis codes in SACT.

Addressing clinical uncertainties

Treatment duration

Treatment duration is calculated from the start of a patient's treatment to their last known treatment date in SACT.

Treatment start date is defined as the date the patient started their CDF treatment. This date is identified as the patient's earliest treatment date in the SACT dataset for the treatment of interest. Data items[8] used to determine a patient's earliest treatment date are:

- Start date of regimen – SACT data item #22
- Start date of cycle – SACT data item #27
- Administration date – SACT data item #34

The earliest of these dates is used as the treatment start date.

The same SACT data items (#22, #27, #34)[7] are used to identify a patient's final treatment date. The latest of these three dates is used as the patient's final treatment date.

Additional explanation of these dates is provided below:

Start date of regimen

A regimen defines the drugs used, their dosage and frequency of treatment. A regimen may contain many cycles. This date is generally only used if cycle or administration dates are missing.

Start date of cycle

A cycle is a period of time over which treatment is delivered. A cycle may contain several administrations of treatment, after each treatment administration, separated by an appropriate time delay. For example; a patient may be on a 3-weekly cycle with treatment being administered on the 1st and 8th day, but nothing on days 2 to 7 and days 9 to 20. The 1st day would be recorded as the "start day of cycle". The patient's next cycle would start on the 21st day.

Administration date

An administration is the date a patient is administered the treatment, which should coincide with when they receive treatment. Using the above example, the administrations for a single 3-week cycle would be on the 1st and 8th day. The next administration would be on the 21st day, which would be the start of their next cycle.

The interval between treatment start date and final treatment date is the patient's time on treatment.

All patients are then allocated a 'prescription length', which is a set number of days added to the final treatment date to allow for the fact that they are effectively still 'on treatment' between administrations. The prescription length should correspond to the typical interval between treatment administrations.

If a patient dies between administrations, then their censor date is their date of death and these patients are deemed to have died on treatment unless an outcome summary is submitted to the SACT database confirming that the patient ended treatment due to disease progression or toxicity before death.

Fedratinib is administered orally. As such, treatment is generally administered in a healthcare facility and healthcare professionals can confirm that the prescribing of treatment has taken place on a specified date. A duration of 28 days has been added to the final treatment date for all patients; this represents the duration from a patient's last cycle to their next[9]. Fedratinib is a 28-day cycle consisting of one administration of 28 tablets[8].

Treatment duration is calculated for each patient as:

Treatment duration (days) = (Final treatment date – Treatment start date) + prescription length (days). This date would be the patient's censored date, unless a patient dies in between their last treatment and the prescription length added, in this case, the censored date would be the patients date of death.

Once a patient's treatment duration has been calculated, the patient's treatment status is identified as one of the following:

No longer receiving treatment (event), if:

- the patient has died.
- the outcome summary, detailing the reason for stopping treatment has been completed:
    - SACT v2.0 data item #41
    - SACT v3.0 data item #58 - #61.
- there is no further SACT records for the patient following a three-month period.

If none of the above apply, the patient is assumed to still be on treatment and is censored.

Overall survival (OS)

OS is calculated from the CDF treatment start date, not the date of a patient's cancer diagnosis. Survival from the treatment start date is calculated using the patient's earliest treatment date, as described above, and the patient's date of death or the date the patient was traced for their vital status.

All patients in the cohort of interest are submitted to the PDS to check their vital status (dead or alive). Patients are traced before any analysis takes place. The date of tracing is used as the date of follow-up (censoring) for patients who have not died.

OS is calculated for each patient as the interval between the earliest treatment date where a specific drug was given to the date of death or date of follow-up (censoring).

OS (days) = Date of death (or follow up) - treatment start date

The patient is flagged as either:

Dead (event):

At the date of death recorded on the PDS.

Alive (censored):

At the date patients were traced for their vital status as patients are confirmed as alive on this date.

Lost to follow-up:

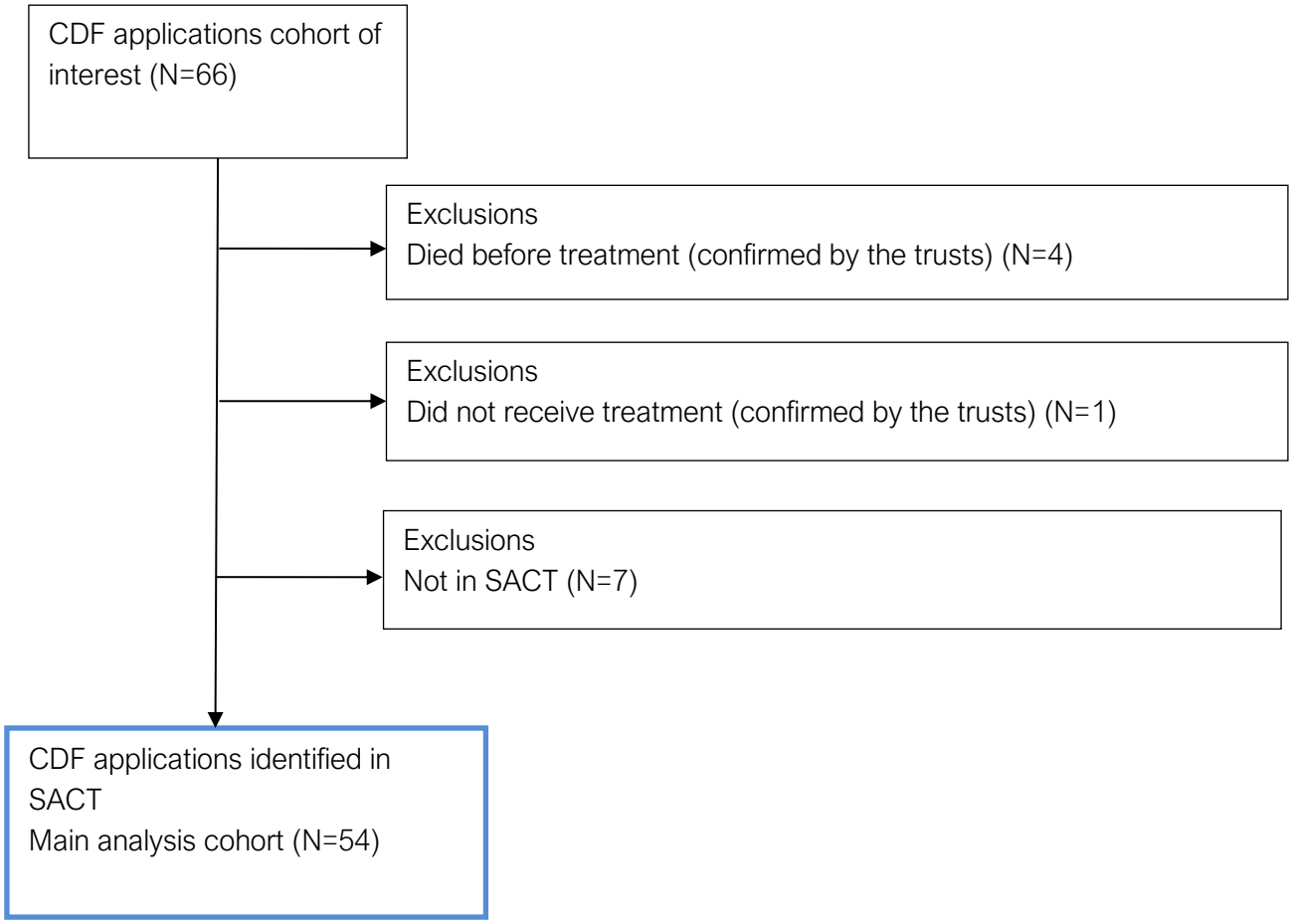
Where we cannot determine whether a patient is alive or not on the censor date; this happens when a patient cannot be successfully traced, for example, because they have emigrated or because important identifiers such as NHS number or date of birth contain errors, the patient's record will be censored at their last known treatment date in SACT. This is the date the patient was last known to be alive.

4. Results

Cohort of interest

Of the 66 applications for CDF funding for fedratinib for the treatment of disease-related splenomegaly or symptoms in myelofibrosis, one patient did not receive treatment, four patients died before treatment and seven patients were missing from SACT[a] (see Figure 2).

Figure 2: Matched cohort - SACT data to CDF (Blueteq®) applications for fedratinib for the treatment of disease-related splenomegaly or symptoms in myelofibrosis between 17 November 2021 and 31 October 2022.



[a] The one patient who did not receive treatment and the four patients who died before treatment, all were confirmed by the relevant trust by the SACT data liaison team.

A maximum of 61 fedratinib records are expected in SACT for patients who were alive, eligible and confirmed to have commenced treatment (Figure 2). 89% (54/61) of these applicants for CDF funding have a treatment record in SACT.

Completeness of SACT key variables

Table 1 presents the completeness of key data items required from SACT. Completeness is 100% for primary diagnosis, date of birth, gender, start date of regimen and start date of cycle. Administration date is 98% complete and performance status at the start of regimen is 52% complete.

Table 1: Completeness of key SACT data items for the fedratinib cohort (N=54)

Variable	Completeness (%)
Primary diagnosis	100%
Date of birth (used to calculate age)	100%
Gender	100%
Start date of regimen	100%
Start date of cycle	100%
Administration date	98%
Performance status at start of regimen	52%

Table 2 presents the completeness of regimen outcome summary. A patient's outcome summary, detailing the reason why treatment was stopped, is only captured once a patient has completed their treatment. Therefore, the percentage completeness provided for outcome summary is for records where we assume treatment has stopped and an outcome is expected. Outcomes are expected if a patient has died, has an outcome in SACT stating why treatment has ended or has not received treatment with fedratinib in at least three months[9]. These criteria are designed to identify all cases where a patient is likely to have finished treatment. Based on these criteria, outcomes are expected for 27 patients. Of these, 24 (89%) have an outcome summary recorded in the SACT dataset.

Table 2: Completeness of outcome summary for patients that have ended treatment (N=27)

Variable	Completeness (%)
Outcome summary of why treatment was stopped	89%

Completeness of Blueteq key variables

Table 3 presents the completeness of key data items required from Blueteq.

Table 3: Completeness of Blueteq key variables (N=54)

Variable	Completeness (%)
Diagnosis of primary myelofibrosis	100%
Risk category	100%
Previously treated with ruxolitinib	100%

Patient characteristics

The median age of the 54 patients receiving fedratinib for the treatment of disease-related splenomegaly or symptoms in myelofibrosis was 72 years. The median age in males and females was 73 and 72 years respectively.

Table 4: Patient characteristics (N=54)

Patient characteristics[b]			
		N	%
Gender	Male	41	76%
	Female	13	24%
Age	<40	2	4%
	40 to 49	2	4%
	50 to 59	4	7%
	60 to 69	14	26%
	70 to 79	26	48%
	80+	6	11%
Performance status at the start of regimen	0	8	15%
	1	15	28%
	2	5	9%
	3	0	0%
	4	0	0%

[b] Figures may not sum to 100% due to rounding.

Patient characteristics[b]			
	Missing	26	48%

Blueteq data items

Table 5 shows the distribution of Blueteq data items with 30 (56%) patients having a diagnosis of primary myelofibrosis, 12 (22%) patients were diagnosed with post polycythaemia vera myelofibrosis and 12 (22%) patients were diagnosed with post essential thrombocythaemia myelofibrosis.

Majority of patients, 37 (69%) had a myelofibrosis risk category of intermediate-2 and 17 (31%) patients had high-risk category myelofibrosis.

Patients were previously treated with ruxolitinib, of which, disease progression on ruxolitinib occurred in 41 (76%) patients and 13 (24%) patients had an intolerance to ruxolitinib.

Table 5: Distribution of key Blueteq data items (N=54)

Blueteq data items[c]		N	%
Diagnosis of primary myelofibrosis	Primary myelofibrosis	30	56%
	Post polycythaemia vera myelofibrosis	12	22%
	Post essential thrombocythaemia myelofibrosis	12	22%
Risk category	Intermediate-2	37	69%
	High risk	17	31%
Previously treated with ruxolitinib	Disease progression on ruxolitinib	41	76%
	Patient intolerance of ruxolitinib	13	24%

[c] Figures may not add to 100% due to rounding.

Treatment duration

Of the 54 patients with CDF applications, 27 (50%) were identified as having completed treatment by 31 October 2022 (latest follow up in SACT dataset). Patients are assumed to have completed treatment if they have died, have an outcome summary recorded in the SACT dataset or they have not received treatment with fedratinib in at least three months (see Table 10). The median follow-up time in SACT was 4.6 months (140 days). The median follow-up time in SACT is the patients' median observed time from the start of their treatment to their last treatment date in SACT plus the prescription length.

Presently, 94% (N=132) of trusts submit their SACT return to the submission portal two months after the month's treatment activity has ended; this provides a maximum follow-up period of 11 months. 6% (N=9) of trusts submit their SACT return to the submission portal one month after the month's treatment activity has ended; this provides a maximum follow-up period of 12 months. SACT follow-up ends 31 October 2022.

Table 6: Breakdown by patients' treatment status [d,e,f]

Patient status	Frequency (N)	Percentage (%)
Patient died – not on treatment	12	22%
Patient died – on treatment	7	13%
Treatment stopped	8	15%
Treatment ongoing	27	50%
Total	54	100%

Table 7: Treatment duration at 6 and 12-month intervals

Time period	Treatment duration (%)
6 months	50% [95% CI: 34%, 64%]
12 months	29% [95% CI: 13%, 48%]

[d] Figures may not sum to 100% due to rounding.
[e] Table 10 presents the outcome summary data reported by trusts. This includes patients from Table 6 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[f] 'Deaths on treatment' and 'deaths not on treatment' are explained in the methodology paper available on the SACT website: http://www.chemodataset.nhs.uk/nhse_partnership/.

The Kaplan-Meier curve for treatment duration is shown in Figure 3. The median treatment duration for all patients was 5.7 months [95% CI: 3.9, 9.7] (173 days).

Figure 3: Kaplan-Meier treatment duration (N=54)

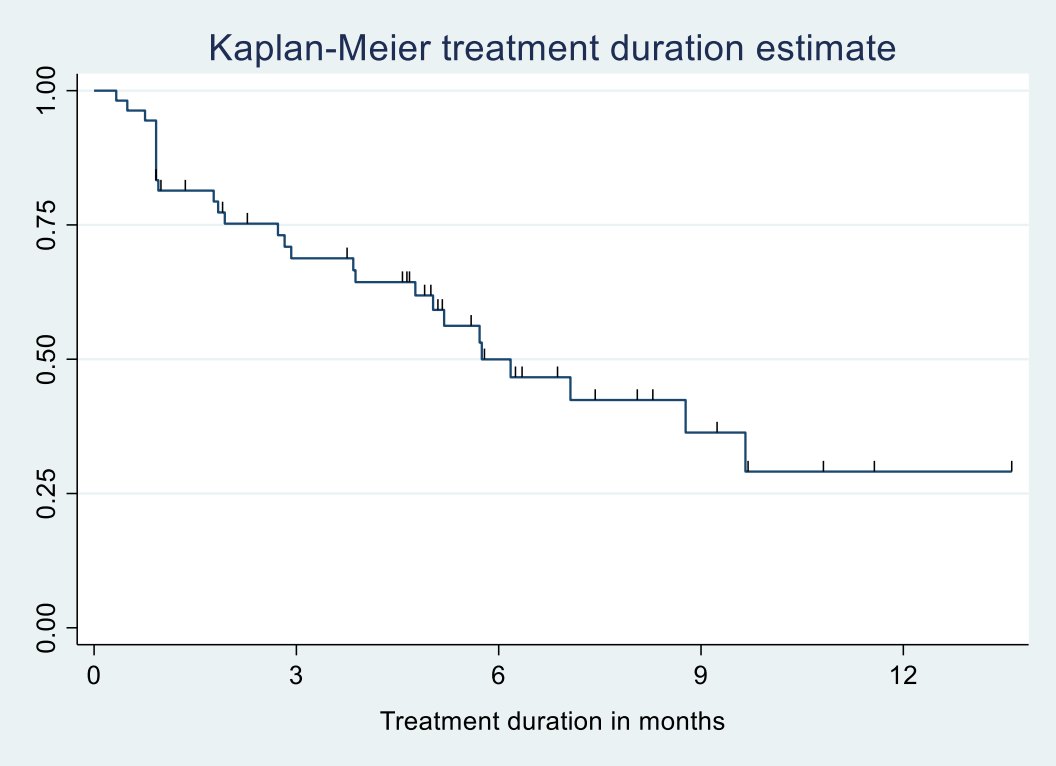


Table 8 and Table 9 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 11.4 months (346 days). SACT contains more follow-up for some patients.

Table 8: Number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-12	3-12	6-12	9-12	12
Number at risk	54	32	15	6	1

Table 9 shows that for all patients who received treatment, 27 were still on treatment (censored) at the date of follow-up and 27 had ended treatment (events).

Table 9: Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored)

Time intervals (months)	0-12	3-12	6-12	9-12	12
Censored	27	21	11	5	1
Events	27	11	4	1	0

Table 10 gives a breakdown of a patient's treatment outcome recorded in SACT when a patient's treatment has come to an end. 50% (N=27) of patients had ended treatment at 31 October 2022.

Table 10: Treatment outcomes for patients that have ended treatment (N=27)[g,h]

Outcome	Frequency (N)	Percentage (%)
Stopped treatment – acute toxicity	7	26%
Stopped treatment – died on treatment	7	26%
Stopped treatment – progression of disease	6	22%
Stopped treatment – died not on treatment[i]	5	19%
Stopped treatment – patient choice	2	7%
Total	27	100%

[g] Figures may not sum to 100% due to rounding.
[h] Table 10 presents the outcome summary data reported by trusts. This includes patients from Table 6 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[i] 'Deaths on treatment' and 'deaths not on treatment are explained in the methodology paper available on the SACT website.

Table 11: Treatment outcomes and treatment status for patients that have ended treatment (N=27)

Outcome[j]	Patient died [k] not on treatment	Treatment stopped	Patient died on treatment
Stopped treatment – acute toxicity	2	5	
Stopped treatment – died on treatment			7
Stopped treatment – progression of disease	5	1	
Stopped treatment – died not on treatment[l]	5		
Stopped treatment – patient choice		2	
Total	12	8	7

[j] Relates to outcomes submitted by the trust in Table 10.
[k] Relates to treatment status in Table 6 for those that have ended treatment.
[l] 'Deaths on treatment' and 'deaths not on treatment are explained in the methodology paper available on the SACT website.

Overall survival (OS)

Of the 54 patients with a treatment record in SACT, the minimum follow-up was 3.4 months (103 days) from the last CDF application. Patients were traced for their vital status on 13 February 2023. This date was used as the follow-up date (censored date) if a patient is still alive. The median follow-up time was 7.5 months (228 days). The median follow-up is the patients' median observed time from the start of their treatment to death or censored date.

Table 12: OS at 6 and12-month intervals

Time period	OS (%)
6 months	74% [95% CI: 59%, 83%]
12 months	57% [95% CI: 40%, 71%]

Figure 4 provides the Kaplan-Meier curve for OS, censored at 13 February 2023. The median OS was not reached.

Figure 4: Kaplan-Meier survival plot (N=54)

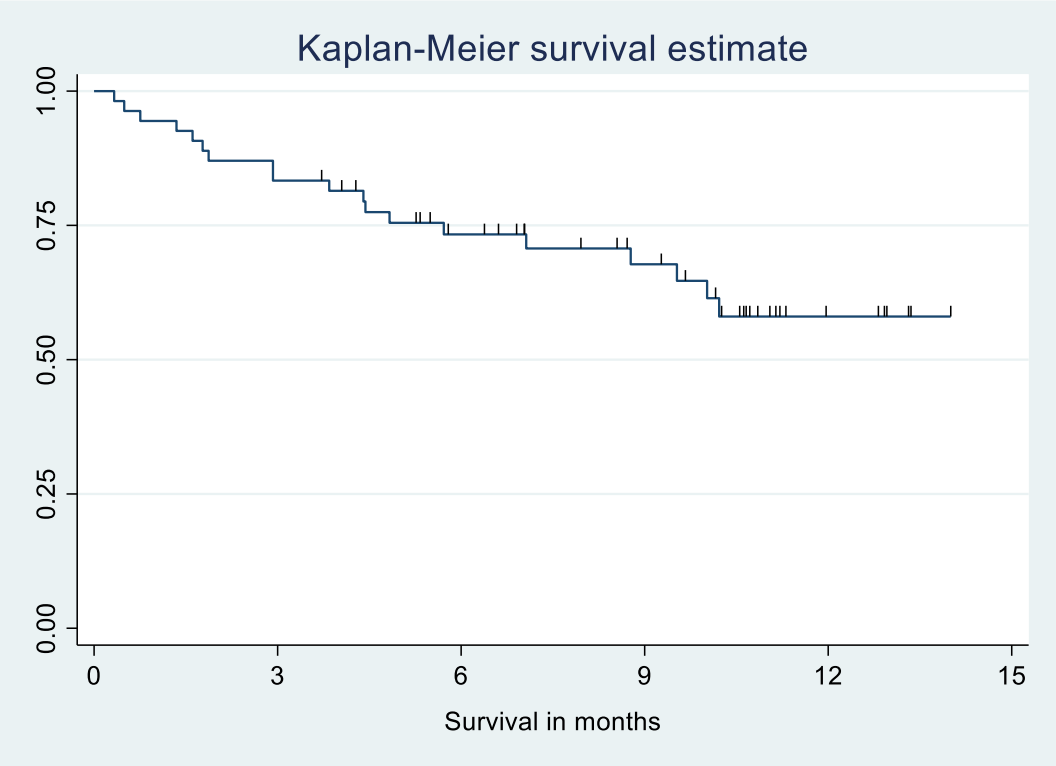


Table 13 and Table 14 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 14.9 months (453 days), all patients were traced on 13 February 2023.

Table 13: Includes the number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-15	3-15	6-15	9-15	12-15
Number at risk	54	45	33	23	6

Table 14 shows that for all patients who received treatment, 35 were still alive (censored) at the date of follow-up and 19 had died (events).

Table 14: Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints

Time intervals (months)	0-15	3-15	6-15	9-15	12-15
Censored	35	35	28	20	6
Events	19	10	5	3	0

5. Sensitivity analyses

6-months follow up

Treatment duration

Sensitivity analyses were carried out on a cohort with at least six months follow-up in SACT. To identify the treatment duration cohort, CDF applications were limited from 17 November 2021 to 30 April 2022 and SACT activity was followed up to the 31 October 2022.

Following the exclusions above, 32 patients (59%) were identified for inclusion. The median follow-up time in SACT was 5.7 months (173 days). The median follow-up time in SACT is the patients' median observed time from the start of their treatment to their last treatment date in SACT plus the prescription length.

The Kaplan-Meier curve for treatment duration is shown in Figure 5. The median treatment duration for patients in this cohort was 5.7 months [95% CI: 2.9, 9.7] (173 days) (N=32).

Figure 5: Kaplan-Meier treatment duration plot (N=32)

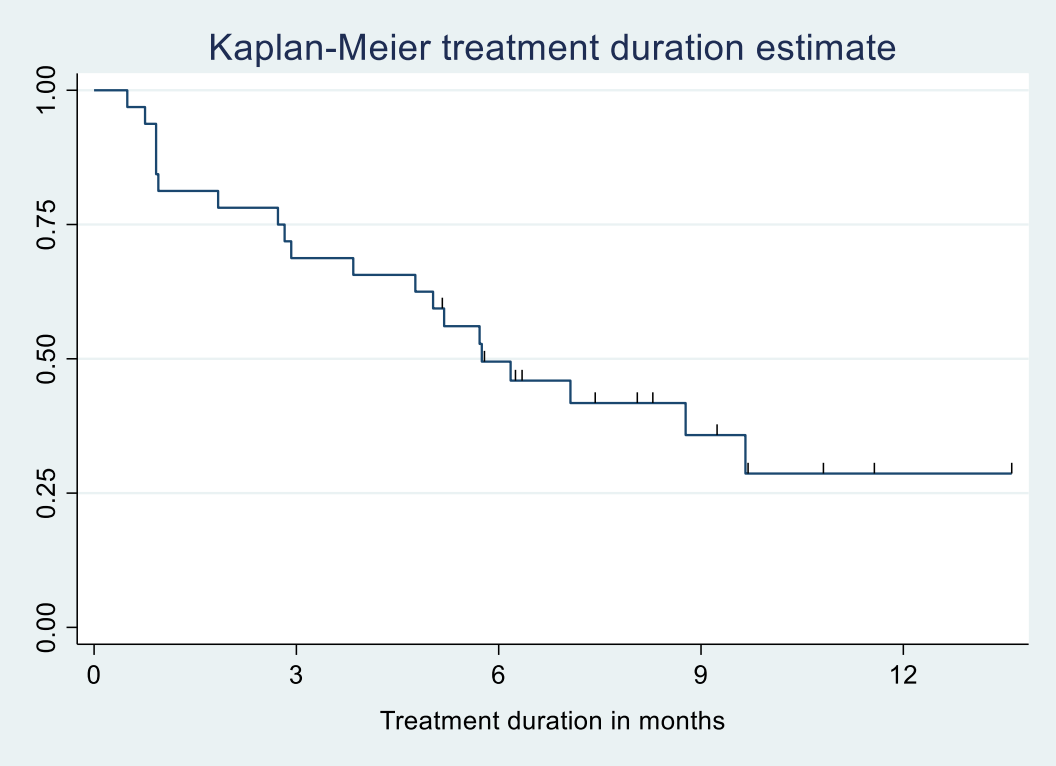


Table 15 and Table 16 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 11.4 months (346 days). SACT contains more follow-up for some patients.

Table 15: Includes the number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-12	3-12	6-12	9-12	12
Number at risk	32	22	14	6	1

Table 16 shows that for all patients who received treatment, 12 were still on treatment (censored) at the date of follow-up and 20 had ended treatment (events).

Table 16: Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored)

Time intervals (months)	0-12	3-12	6-12	9-12	12
Censored	12	12	10	5	1
Events	20	10	4	1	0

Overall survival (OS)

Sensitivity analyses was also carried out for OS on a cohort with at least six months follow-up. To identify the cohort, CDF applications were limited from 17 November 2021 to 13 August 2022 and patients were traced for their vital status on 13 February 2023.

Following the exclusions above, 43 patients (80%) were identified for inclusion. The median follow-up time was 9.5 months (289 days).

The median follow-up is the patients' median observed time from the start of their treatment to death or censored date.

The Kaplan-Meier curve for OS is shown in Figure 6. The median OS for patients in this cohort was not reached.

Figure 6: Kaplan-Meier survival plot (N=43)

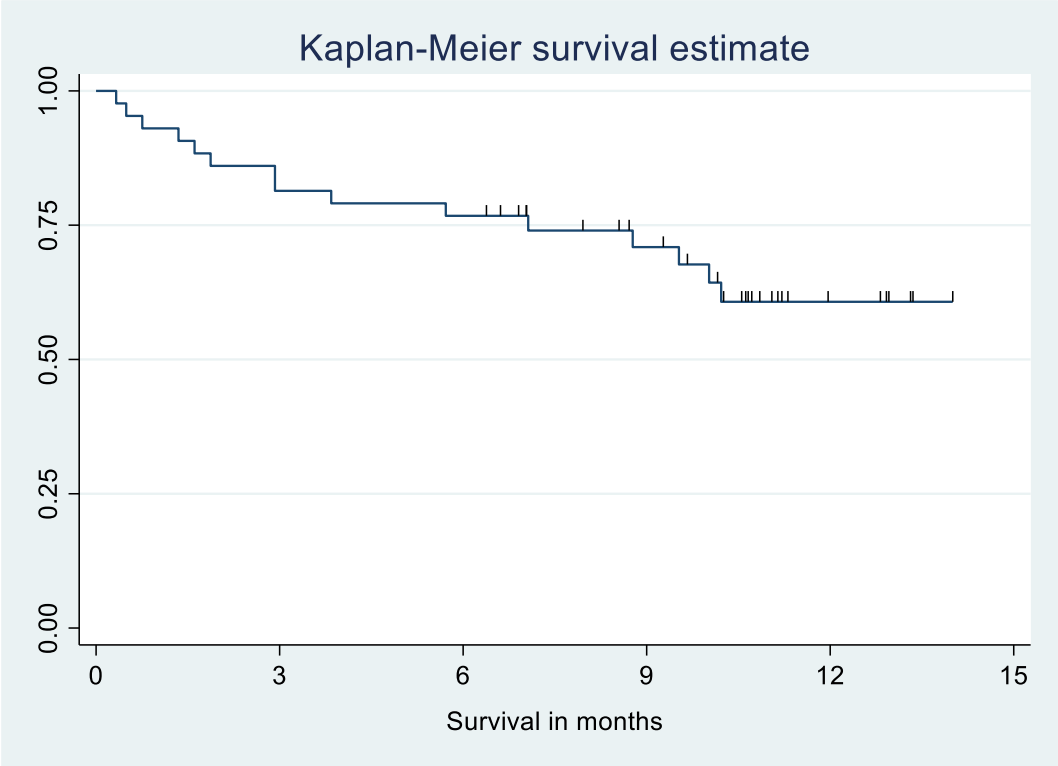


Table 17 and Table 18 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 14.9 months (453 days), all patients were traced on 13 February 2023.

Table 17: Includes the number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-15	3-15	6-15	9-15	12-15
Number at risk	43	35	33	23	6

Table 18 shows that for all patients who received treatment, 28 were still alive (censored) at the date of follow-up and 15 had died (events).

Table 18: Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints

Time intervals (months)	0-15	3-15	6-15	9-15	12-15
Censored	28	28	28	20	6
Events	15	7	5	3	0

Table 19: Median treatment duration and OS, full cohort and sensitivity analysis

Metric	Main CDF cohort Standard analysis: Full cohort	Sensitivity analysis: 6 months follow-up cohort: treatment duration	Sensitivity analysis: 6 months follow-up cohort: OS
N	54	32	43
Median treatment duration	5.7 months [95% CI: 3.9, 9.7] (173 days).	5.7 months [95% CI: 2.9, 9.7] (173 days).	
OS	Not reached		Not reached

6. Conclusions

61 patients received fedratinib for the treatment of disease-related splenomegaly or symptoms in myelofibrosis [TA756] through the CDF in the reporting period (17 November 2021 and 31 October 2022). 54 patients were reported to the SACT dataset, giving a SACT dataset ascertainment of 89%. An additional patient with a CDF application did not receive treatment and four patients died before treatment. The patient who did not receive treatment and the four patients identified as a death before treatment were confirmed by the trust responsible for the CDF application by the team at NHS England.

Patient characteristics from the SACT dataset show that 76% (N=41) of patients who received fedratinib for the treatment of disease-related splenomegaly or symptoms in myelofibrosis were male and 24% (N=13) of patients were female. Most of the cohort was aged between 60 and 79 years 74%, (N=40) and 52% (N=28) of patients had a performance status between 0 and 2 at the start of their regimen.

At data cut off, 50% (N=27) of patients were identified as no longer being on treatment. Of these 27 patients:

- 26% (N=7) of patients stopped treatment due to acute toxicity
- 26% (N=7) of patients died on treatment
- 22% (N=6) of patients stopped treatment due to disease progression
- 19% (N=5) of patients died not on treatment
- 7% (N=2) of patients chose to end their treatment

Median treatment duration was 5.7 months [95% CI: 3.9, 9.7] (173 days). 50% of patients were still receiving treatment at 6 months [95% CI: 34%, 64%] and 29% of patients were still receiving treatment at 12 months [95% CI: 13%, 48%].

The median OS was not reached. OS at 6 months was 74% [95% CI: 59%, 83%] and 12 months OS was 57% [95% CI: 40%, 71%].

Sensitivity analysis was carried out on treatment duration and OS to evaluate a cohort for which all patients had a minimum follow-up of six months. Results for both treatment duration and OS was the same as the full cohort.

7. References

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8. Addendum

Fedratinib for treating disease-related splenomegaly or symptoms in myelofibrosis (TA756)

Subsequent to provision of the initial draft of this report to NICE and Bristol Myers Squibb Pharmaceuticals Ltd, NHS England were requested to refresh overall survival for the original cohort.

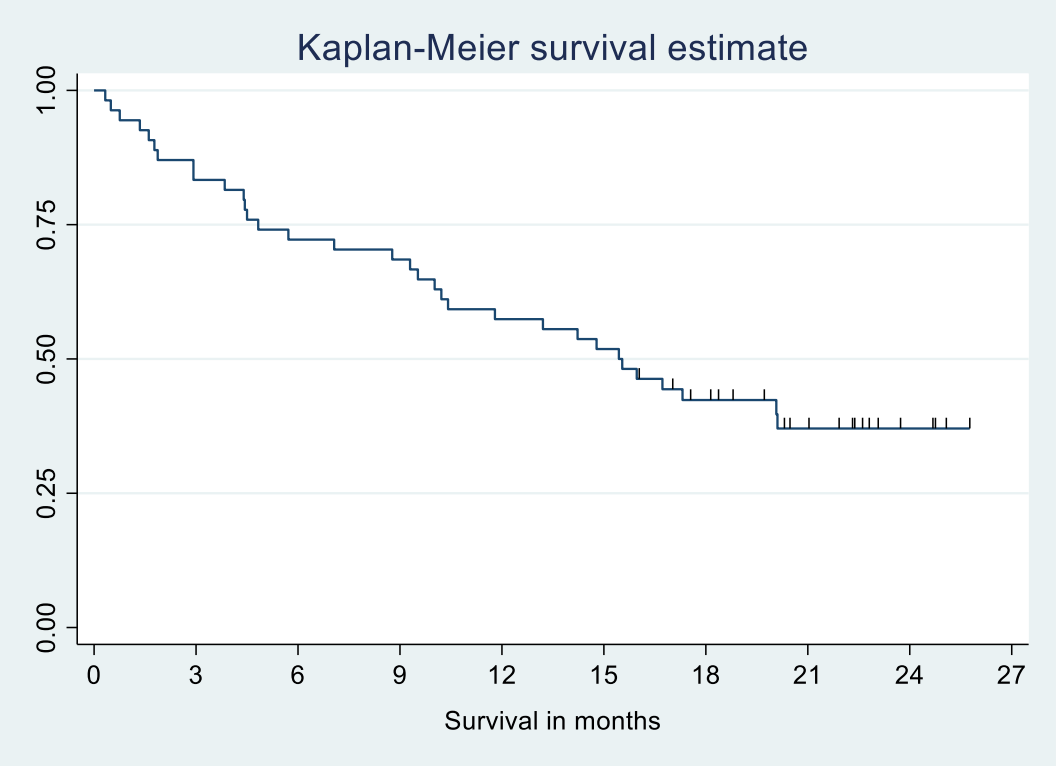
All 54 patients were re-traced for their vital status on 5 February 2024. This date was used as the follow-up date (censored date) if a patient is still alive. The median follow-up time was 15.5 months (471 days). The median follow-up is the patients' median observed time from the start of their treatment to death or censored date.

Table 1: OS at 6, 12, 18 and 24-month intervals

Time period	OS (%)
6 months	72% [95% CI: 58%, 82%]
12 months	57% [95% CI: 43%, 69%]
18 months	42% [95% CI: 29%, 55%]
24 months	36% [95% CI: 23%, 50%]

Figure 1 provides the Kaplan-Meier curve for OS, censored at 5 February 2024. The median OS was 15.4 months[m] (468 days)

Figure 1: Kaplan-Meier survival plot (N=54)



[m] Confidence intervals could not be produced as there was an insufficient number of events at the time this report was produced.

Table 2 and Table 3 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 26.6 months (809 days), all patients were traced on 5 February 2024.

Table 2: Includes the number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-27	3-27	6-27	9-27	12-27	15-27	18-27	21-27	27-27
Number at risk	54	45	39	37	31	28	20	11	4

Table 3 shows that for all patients who received treatment, 21 were still alive (censored) at the date of follow-up and 33 had died (events).

Table 3: Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints

Time intervals (months)	0-27	3-27	6-27	9-27	12-27	15-27	18-27	21-27	27-27
Censored	21	21	21	21	21	21	18	11	4
Events	33	24	18	16	10	7	2	0	0

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Fedratinib for treating disease-related splenomegaly or symptoms in myelofibrosis (Review of TA756) [ID5115]

Clinical expert statement

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Part 1: Treating myelofibrosis and current treatment options

Table 1 About you, aim of treatment, place and use of fedratinib, sources of evidence and equality

1. Your name	Tim Somervaille
2. Name of organisation	The Christie NHS Foundation Trust
3. Job title or position	Honorary Consultant in Haematology
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with myelofibrosis? ☒ A specialist in the clinical evidence base for myelofibrosis or fedratinib? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for myelofibrosis ? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	There are multiple goals of treatment in myelofibrosis which depend on the age and disease status of the patient. Myelofibrosis is a very heterogeneous disease. The range of desired outcomes can include the goal of cure where you have a

	younger fitter patient with high-risk disease; here one should consider the possibility of allogeneic transplantation. Much more frequently the goal of therapy is to improve quality of life and to reduce the impact of disease-associated symptoms on the individual patient. Some patients have anaemia as their main issue and historically we have tried to mitigate that with erythropoietic injections, drugs such as danazol, or blood transfusions, and more recently momelotinib. Other patients have issues relating to sweats, weight loss, itching and/or a bulky uncomfortable spleen, and these patients typically do well with JAK2 inhibitors such as ruxolitinib, fedratinib or momelotinib. There is a widespread feeling in the MPN physician community (and some evidence from the original COMFORT trials) that JAK inhibitors prolong survival in patients who are unwell with symptoms from their disease, in particular in those who go on to have a good symptomatic and spleen response to treatment.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	This varies from patient to patient, depending on their disease status, but would include: Symptom improvement: reduction in symptoms like fatigue, night sweats, weight loss, itching and bone pain (as measured by a scale such as MPN-SAF). Splenomegaly reduction: decrease in spleen size, often measured through physical examination or imaging studies, thereby reducing discomfort or pain arising from an enlarged spleen. Anaemia management: improvement in anaemia, evidenced by increased haemoglobin levels and a reduced need for blood transfusions. Blood count normalization: improvement or normalization of blood counts, including platelets and white blood cells, which are often affected by myelofibrosis. Other items might include reduced marrow fibrosis or reduced variant allele frequency, and improved survival.

10. In your view, is there an unmet need for patients and healthcare professionals in myelofibrosis?	Yes, absolutely. Additional first line options for treatment of myelofibrosis would be welcome to increase clinician and patient choice. In the future we need novel treatments which alter disease trajectory and enhance survival.
11. How is myelofibrosis currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	MF is managed in the UK as per the BCSH's recently updated guideline on ***diagnosis*** shown here: https://pubmed.ncbi.nlm.nih.gov/37932932/ and ***treatment*** shown here: https://pubmed.ncbi.nlm.nih.gov/38037886/ The pathway of care is generally well defined and is as outlined in the above-mentioned United Kingdom guidelines. The authors are UK clinicians experienced in the treatment of myelofibrosis. MF patients with symptoms and/or an enlarged spleen generally benefit in terms of symptom response and spleen volume reduction with a JAK2 inhibitor such as ruxolitinib, momelotinib or fedratinib. The availability of fedratinib as an alternative to ruxolitinib or momelotinib in first line treatment of myelofibrosis will make a significant difference for patients with myelofibrosis. For example, fedratinib would provide an alternative up front therapy for patients who might not respond well to or tolerate ruxolitinib or momelotinib.
12. Will fedratinib be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Fedratinib is an effective treatment for disease-related symptoms and splenomegaly in myelofibrosis and would therefore be used in a similar way to existing JAK2 inhibitors in UK clinical practice. I would expect fedratinib only to be prescribed by a clinical haematologist experienced in the treatment of patients with myelofibrosis. Consequently its use would only be through or in close collaboration with a specialist centre. No additional investment will be required for its introduction in terms of facilities or equipment; considerations for the use of fedratinib by the prescribing physician are outlined in the BCSH guidelines mentioned above.

13. Do you expect fedratinib to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Fedratinib is an effective treatment for disease-related symptoms and splenomegaly in myelofibrosis. Its availability for treatment of JAK2 inhibitor naïve patients in the United Kingdom (it has been available in the US as up front therapy since August 2019) will enhance patient and clinician treatment choice. While it is always challenging to compare disease responses across separate clinical trials and separate cohorts of patients, it seems likely that fedratinib offers at least similar levels of spleen volume reduction by comparison with ruxolitinib and momelotinib in intermediate-2 and high risk MF patients needing first line JAK inhibitor therapy. Further it also seems probable that fedratinib offers at least similar levels of symptomatic improvement by comparison with ruxolitinib. The prior randomized SIMPLIFY1 study demonstrated that momelotinib was not as effective as ruxolitinib in conferring symptomatic improvement. Whatever the benefits of ruxolitinib in terms of increase in length of life and quality of life, I would expect fedratinib to match that.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Each JAK2 inhibitor has its strengths and weaknesses which guide the choice of JAK2 inhibitor for each specific patient. Ruxolitinib typically confers significant improvement in symptoms and spleen volume. However its use is associated with anaemia, thrombocytopaenia, weight gain, a risk of latent virus reactivation and an increased risk of skin cancer, some of which can be aggressive. While momelotinib confers similar levels of spleen volume reduction the level of symptomatic improvement is inferior compared with ruxolitinib. The real strength of momelotinib is that in anaemic MF patients some significant anaemia responses leading to avoidance of or independence from blood transfusion. This means that in the UK currently (June 2024) a myelofibrosis patient requiring JAK2 inhibitor treatment for the first time is likely to be offered momelotinib if their haemoglobin is less than around 90 g/L or ruxolitinib if higher than that. Fedratinib confers strong spleen volume reduction and symptomatic improvement either up front or following failure of ruxolitinib as evidenced by the

	original JAKARTA studies. In addition to anaemia and thrombocytopaenia (somewhat similar to ruxolitinib), the weakness of fedratinib is that - at least to start with - patients can suffer with gastrointestinal side effects including nausea vomiting and diarrhoea. These adverse effects tend to settle with ongoing therapy. Importantly, fedratinib is not associated with weight gain and so might be a better choice of therapy in patients with high BMI although of course no prospective comparative trial data are available. In contrast, both ruxolitinib and fedratinib would probably be inferior choices of first line JAK2 inhibitor for an MF patient with significant anaemia (<90g/L). Also neither is approved for patients with significant thrombocytopaenia (<50x10^9/L) while there is published experience for the use of momelotinib in patients with platelet counts as low as 25x10^9/L. Fedratinib is a relatively pure JAK2 inhibitor which also inhibits FLT3. By comparison ruxolitinib and momelotinib offer significant JAK1 and JAK2 inhibition which may potentially make ruxolitinib and momelotinib more immunosuppressive than fedratinib. It remains to be seen whether the concerns around skin cancer risk seen with ruxolitinib apply equally to fedratinib.
15. Will fedratinib be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Overall I expect that fedratinib will be no more or no less difficult to use then existing JAK2 inhibitors in MF. Perhaps the most significant issue is the story of potential Wernicke's encephalopathy which arose during the original JAKARTA studies leading to an FDA hold of fedratinib's development from 2013 until 2017. The original study report suggested a 1.3% incidence of Wernicke's or a syndrome similar to that. However, in the intervening time those cases have been carefully evaluated and reviewed, and it would appear that only one definitive Wernicke's case was identified and that that subject had 10% weight loss, poor performance status and ataxia pre-enrolment suggesting prior neurodegeneration. During the study, the subject had uncontrolled GI toxicity without supplementary nutrition, illustrating prior risk factors (see summary in Mullally et al., Blood Advances,

	2020 - PMID: 32343799). Further all suspected WE cases were on a 500mg daily dose, rather than the current standard 400mg daily dose. The conclusion of the review was that there was no evidence that fedratinib causes Wernicke's but that proactive management of GI symptoms to ensure adequate nutrition and measurement of thiamine and thiamine replacement was required, as indicated with the "black box warning." This past series of events has led to a requirement to measure thiamine levels ahead of and during therapy which can add a burden to the management of patients on fedratinib. That said, there is no evidence that a pragmatic approach of concomitant thiamine supplementation for as long the patient is on fedratinib is inferior; and in fact may be superior.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The expected start and stop rules would and should be similar to those for other JAK2 inhibitors ruxolitinib and momelotinib, and as elaborated in the above mentioned BCSH guidance.
17. Do you consider that the use of fedratinib will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	No.
18. Do you consider fedratinib to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition?	While this technology is not a step change in the management of myelofibrosis by comparison with already NICE-approved ruxolitinib and momelotinib, its availability within the UK will significantly widen patient and clinician choice for reasons already elaborated above.

• Does the use of the technology address any particular unmet need of the patient population?	
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	As mentioned above and there is a risk of nausea, vomiting and diarrhoea in the initial weeks of therapy which can effectively be managed with antiemetics and loperamide. Taking fedratinib with a fatty meal can also be helpful in reducing the risk of nausea. My practice is to supply patients with a daily dose of thiamine to take with fedratinib as a pragmatic approach to mitigate risk of Wernicke's, if that even exists on the standard 400mg daily dose. I also ensure that patients have contact details of our chemotherapy hotline so as to flag up any issues with persistent vomiting or other gastrointestinal adverse effects. These are however in my experience only an issue for a small minority of patients, with the vast majority doing very well indeed on treatment.
20. Do the clinical trials on fedratinib reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes. The key trials are JAKARTA and JAKARTA2. A proportion of patients were enrolled from the UK. As with all clinical trials a number of less fit patients might have been excluded but I do not think that that practically affects their conclusions in any significant way. The most important outcomes of the trials were that fedratinib is effective in reducing spleen volume and in improving symptoms. There are no frequent adverse effects not apparent from the clinical trials as far as I am aware, although there is some emerging concern about a rare association with uveitis.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA386, TA957]?	No.

23. How do data on real-world experience compare with the trial data?	I have treated perhaps 15 patients with fedratinib. I took part as a Principal Investigator in the original JAKARTA study and continue as a Principal Investigator for the FREEDOM2 and FEDORA studies. After NICE made fedratinib available in the United Kingdom for MF patients who had failed ruxolitinib (TA756) I treated several patients for this indication on the NHS. My view is that fedratinib is a good drug for up front treatment of myelofibrosis and also for some patients who have failed ruxolitinib, in keeping with published clinical trials. Certainly I have patients now alive and with a good quality of life – after failing ruxolitinib - who owe that to the clinical trial availability of fedratinib on FREEDOM2. The four patients I treated on the original JAKARTA study all had fantastic responses and we were devastated when the trial was prematurely terminated due to the FDA hold. That said I found switching patients who had failed ruxolitinib onto fedratinib much more of a challenge in “real world” practice than perhaps the clinical trials suggested. This may be related to the requirement for a successful JAK2 inhibitor washout period ahead of clinical trial enrolment for the JAKARTA2 and FREEDOM2 studies which some patients cannot tolerate such is the explosive nature of their disease. Of course in real world practice it is precisely these patients who have aggressive disease in whom you consider switching. Published studies reflect these observations – e.g. PMID: 37839939, 37991002, 35614565.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.	No.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Fedratinib is an effective first line therapy for patients with intermediate-2 or high risk myelofibrosis who need treatment

Fedratinib likely delivers at least similar rates of spleen volume reduction as compared with both ruxolitinib and momelotinib

Fedratinib likely delivers at least similar rates of symptomatic improvement as compared with ruxolitinib

AEs in some patients at start of fedratinib (nausea, vomiting and diarrhoea) treatment are typically transient and effectively managed with e.g. cyclizine and loperamide

The risk of Wernicke's, if it exists at the 400mg dose, is mitigated by concomitant use of thiamine or routine plasma monitoring

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Fedratinib for treating disease-related splenomegaly or symptoms in myelofibrosis (Review of TA756) [ID5115]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with myelofibrosis or caring for a patient with myelofibrosis. The text boxes will expand as you type.

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NICE National Institute for Health and Care Excellence

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **<insert deadline>.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Patient expert statement

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with myelofibrosis

Table 1 About you, myelofibrosis, current treatments and equality

1. Your name	AndyTattersall
2. Are you (please tick all that apply)	☐ A patient with myelofibrosis? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with myelofibrosis? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	MPN Voice
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:

	Through my voluntary work as an Advocacy Coordinator for MPN Voice, including reading studies and clinical trial reports relating to MF and gathering information from patients on their lived experience of having MF and any existing therapies with which they have been treated. ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☒ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with myelofibrosis? **If you are a carer (for someone with myelofibrosis please share your experience of caring for them**	I have no personal experience of living with myelofibrosis but having been diagnosed with essential thrombocythaemia over 20 years ago, I am well aware of the symptoms of MF and the limited range of treatment options available for it, in view of the possibility that my ET may one day progress to MF
7a. What do you think of the current treatments and care available for myelofibrosis on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	a. While there are a limited number of current treatments for MF available on the NHS, a significant number of patients are, or become in time, either unresponsive to or intolerant of those treatments. Once treatment has had to be discontinued the only remaining option is stem cell transplantation, for which many patients are ineligible due to other health conditions and/or age. Studies have shown that life expectancy for many MF patients declines rapidly once they have stopped receiving treatment. b. I believe that my views on these current treatments and their limitations are similar to those of other people, including patients, their carers and clinicians.
8. If there are disadvantages for patients of current NHS treatments for myelofibrosis (for example, how they are given or taken, side effects of treatment, and any others) please describe these	I agree with the response given in the joint patient organisation submission from MPN Voice and Leukaemia Care.

9a. If there are advantages of fedratinib over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does fedratinib help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	I agree with the response given in the joint patient organisation submission from MPN Voice and Leukaemia Care.
10. If there are disadvantages of fedratinib over current treatments on the NHS please describe these. For example, are there any risks with fedratinib? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I agree with the response given in the joint patient organisation submission from MPN Voice and Leukaemia Care.
11. Are there any groups of patients who might benefit more from fedratinib or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	The lack of alternative treatments for MF in those patients who are unresponsive to or intolerant of current treatments is a particular issue for patients who are not eligible to be considered for stem cell transplantation. This particularly affects those patients who are elderly and/or who have other health conditions. They are less likely to be considered for SCT than younger or fitter patients, due to the risks involved and the high burden of side effects following this procedure. The availability of fedratinib as another treatment option would therefore particularly benefit these groups of patients.
12. Are there any potential equality issues that should be taken into account when considering myelofibrosis and fedratinib? Please explain if you think any groups	As mentioned in point 11 above, there is a significant unmet need for additional treatment options in older patients who, in most cases, are ineligible for stem cell

of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	transplantation as the only potential cure for their MF and who are therefore disadvantaged compared to younger patients. The availability of fedratinib as an additional treatment option would therefore be of particular value to this group of people.
13. Are there any other issues that you would like the committee to consider?	No

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- I agree with the joint patient group submission made by MPN Voice and Leukaemia Care
- There are a limited number of current treatments for myelofibrosis and a significant number of patients are intolerant of or unresponsive to them, with poor outcomes once treatment is discontinued
- Stem cell transplantation is currently the only potential cure for MF but is not an option for many patients, so there remains a significant unmet need for additional treatment options for those patients who have exhausted the range of other treatments currently available
- Older patients are significantly disadvantaged, compared to younger patients, due to their ineligibility for stem cell transplantation once all other treatment options have ended

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Single Technology Appraisal

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Patient expert statement

Part 1: Living with this condition or caring for a patient with myelofibrosis

Table 1 About you, myelofibrosis, current treatments and equality

1. Your name	Jonathan Mathias
2. Are you (please tick all that apply)	☐ A patient with myelofibrosis? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with myelofibrosis? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	MPN Voice
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☒ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert

Patient expert statement

	engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☒ I have not completed part 2 of the statement
6. What is your experience of living with myelofibrosis? **If you are a carer (for someone with myelofibrosis please share your experience of caring for them**	The MPN Voice submission, which I co-authored with my colleague Andy Tattersall covers this and the remaining points in this form.
7a. What do you think of the current treatments and care available for myelofibrosis on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	
8. If there are disadvantages for patients of current NHS treatments for myelofibrosis (for example, how they are given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of fedratinib over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does fedratinib help to overcome or address any of the listed disadvantages of current treatment that**	

you have described in question 8? If so, please describe these	
10. If there are disadvantages of fedratinib over current treatments on the NHS please describe these. For example, are there any risks with fedratinib? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from fedratinib or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering myelofibrosis and fedratinib? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme	

Patient expert statement

Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

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Fedratinib for treating disease-related splenomegaly or symptoms in myelofibrosis (CDF review of TA756) [ID5115]. A Single Technology Appraisal

Produced by	Sheffield Centre for Health and Related Research (SCHARR), The University of Sheffield
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Date completed	Date completed (22/05/2024)

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Declared competing interests of the authors

None of the authors has any conflicts of interest to declare.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Sarah Davis was project lead. Emily Pulsford critiqued the company's search strategy. Katy Cooper summarised and critiqued the clinical effectiveness data reported within the company's submission. Jean Hamilton critiqued the statistical aspects of the submission. Sarah Davis and Andrew Metry critiqued the health economic analysis submitted by the company. All authors were involved in drafting and commenting on the final report.

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CONTENTS

List of tables

List of figures

List of Boxes

Abbreviations

AEs	Adverse event
AESI	Adverse event of special interest
AF	Acceleration factor
AFT	Accelerated failure time
AIC	Akaike information criterion
ALT	Alanine aminotransferase
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
ASCT	Allogeneic stem cell transplant
AST	Aspartate aminotransferase
BAT	Best available therapy
BIC	Bayesian information criterion
BMS	Bristol Myers Squibb
BNF	British National Formulary
BSA	Body surface area
BSH	British Society for Haematology
CADTH	Canadian Agency for Drugs and Technologies in Health
CALR	Calreticulin
CDF	Cancer Drugs Fund
CEAC	Cost-effectiveness acceptability curve
CSR	Clinical study report
CS	Company submission
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
DIPSS	Dynamic International Prognostic Scoring System
DSU	Decision Support Unit
EAG	External Assessment Group
ECOG PS	Eastern Cooperative Oncology Group performance status
eMIT	Electronic market information tool
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30
EORTC-8D	European Organisation for Research and Treatment of Cancer - 8 Dimension
EOC6	End of cycle 6
EQ-5D-3L	EuroQol 5-dimensions - 3-level

EQ-5D-5L	EuroQol 5-dimensions - 5-level
ET	Essential thrombocythaemia
FED	Fedratinib
Hb	Haemoglobin
HMRN	Haematological Malignancy Research Network
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost effectiveness ratio
INMB	Incremental net monetary benefit
IPCW	Inverse probability of censoring weighting
IPE	Iterative parameter estimation
IPSS	International Prognostic Scoring System
IRT	Interactive response technology
ITT	Intention to treat
IWG-MRT	International Working Group - Myeloproliferative Neoplasms Research and Treatment
JAK	Janus associated kinase
JAKi	Janus associated kinase inhibitor
KM	Kaplan-Meier
LCM	Left costal margin
LY	Life year
MFSAF	Myelofibrosis Symptom Assessment Form
MF-8D	Myelofibrosis - 8-Dimension
MHRA	Medicines and Healthcare products Regulatory Agency
MIMS	Monthly Index of Medical Specialities
MPL	Thrombopoietin receptor, also known as TPOR
MRI	Magnetic resonance imaging
NHS	National Health Service
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NR	Not reported
OS	Overall survival
PAS	Patient access scheme
PH	Proportional hazards
PMF	Primary myelofibrosis
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses

PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PV	Polycythaemia
QALY	Quality-adjusted life year
RBC	Red blood cell
RCT	Randomised controlled trial
RDI	Relative dose intensity
RPSFT	Rank-preserving structure failure time
SACT	Systemic Anti-Cancer Therapy
SD	Standard deviation
SDPFS	Spleen and disease progression-free survival
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SPC	Summary of product characteristics
SVR	Spleen volume reduction
TA	Technology Appraisal
TEAE	Treatment-emergent adverse event
TSEgest	Two-stage estimation with g-estimation
TSD	Technical Support Document
TSS	Total symptom score
TTD	Time to treatment discontinuation
ULN	Upper limit of normal
U.S. FDA	United States Food and Drug Administration
TYK2	Tyrosine kinase 2
VAS	Visual analogue scale
VBA	Visual basic application
WHO ICTRP	World Health Organisation International Clinical Trials Registry Platform
WTP	Willingness-to-pay

1. Executive summary

This External Assessment Group (EAG) report assesses fedratinib for the treatment of disease-related splenomegaly or symptoms in myelofibrosis. The company submission (CS) positions fedratinib for use in patients who have previously been treated with ruxolitinib, which is a narrower population than that specified in the NICE scope, but is consistent with the use of fedratinib within the Cancer Drugs Fund (CDF) under the recommendations in Technology Appraisal (TA)756. The CS states that the most relevant comparator for fedratinib in this population is a group of treatments which it terms 'best available therapy' (BAT), which the company considers includes the use of ruxolitinib. The key study informing the CS is the FREEDOM-2 trial which compared fedratinib to BAT, including ruxolitinib, in patients previously treated with ruxolitinib. Supportive data are also provided from the Systemic Anti-Cancer Therapy (SACT) database, which reports data on the real-world use of fedratinib within the CDF.

This summary provides a brief overview of the key issues identified by the EAG as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs) when using list prices for comparator technologies. The cost-effectiveness results when using confidential comparator prices are included in a separate confidential appendix.

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.5 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, and do not necessarily reflect the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Key issues identified by the EAG that potentially impact on the cost-effectiveness estimates for fedratinib versus BAT are summarised in **Error! Reference source not found.**.

Table 1: Overview of EAG's key issues

ID5115	Summary of issue	Report sections
Issue 1	No comparison against momelotinib	2.3.3
Issue 2	The high proportion of patients crossing over from BAT to fedratinib in the comparator arm of FREEDOM-2 makes it difficult to compare outcomes beyond 6 months	3.2.3, 3.3.9
Issue 3	Uncertainty regarding the composition of BAT received after fedratinib	4.3.3.2
Issue 4	Uncertainty regarding the proportion of patients transitioning straight to supportive care after fedratinib	4.3.3.3
Issue 5	Inconsistent assumptions regarding utility gains in non-responders to fedratinib and BAT	4.3.3.4
Issue 6	Costing of ruxolitinib assumes high wastage due to dose changes	4.3.3.5
Issue 7	Uncertainty regarding duration of suboptimal ruxolitinib within BAT (related to Issue 2)	4.3.3.6
Issue 8	Estimates of OS and TTD from FREEDOM-2 may overestimate the time on treatment and OS expected in clinical practice	4.3.3.7

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

- The EAG prefers to assume that the usage of fedratinib in patients failing to respond to, or losing response to fedratinib (termed suboptimal fedratinib) is the same as the usage of ruxolitinib in the BAT comparator arm (termed suboptimal ruxolitinib), whereas the company assumes zero usage of suboptimal fedratinib in both responders and non-responders to fedratinib.
- The company applies a utility gain from baseline for non-responders to fedratinib but zero utility gain for non-responders to BAT, whereas the EAG prefers to assume the same utility gain for all non-responders.
- The EAG prefers to apply the average initial dose distribution across the first 6 cycles in FREEDOM-2, with an additional 5% wastage, based on an assumption considered in TA756, whereas the company assumes a much higher amount of wastage due to dose modifications.
- The EAG prefers to include all drug treatments received within BAT in the model, whereas the company's base-case excludes some treatments received.
- The EAG prefers to assume that the RBC transfusion rate is equal between fedratinib and BAT.
- The EAG has corrected some minor errors identified in the company's model and has incorporated updated drug prices.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length of life (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained. The company's base-case model assumes no difference in overall survival (OS) between patients receiving fedratinib and those receiving BAT, therefore differences in QALYs are driven solely by differences in health-related quality of life (HRQoL).

Overall, in the company's base-case analysis, the technology is modelled to affect QALYs by:

- Increasing the proportion of patients achieving a response to treatment which provides a QALY gain because utility is higher in responders than non-responders
- A higher utility being allocated to non-responders to fedratinib than non-responders to BAT
- Reducing the time spent in the supportive care health state in which utility is assumed to decline every 6 months.

Overall, in the company's base-case analysis, the technology is modelled to affect costs by:

- Decreasing overall drug acquisition costs because the total drug acquisition costs for the fedratinib arm are lower than the total drug acquisition costs for the BAT comparator arm; the high cost of the latter being driven by the high drug wastage assumed for suboptimal ruxolitinib in BAT
- Reducing disease management costs due to lower costs being assumed in the long-term for patients receiving JAK inhibitors (fedratinib or ruxolitinib) versus those receiving other forms of BAT or supportive care
- Fedratinib having requirements for thiamine testing, and supplementation in thiamine deficient patients, which results in a small additional cost

The modelling assumptions that have the greatest effect on the ICER are:

- The assumptions regarding drug wastage for ruxolitinib patients having dose adjustments
- The assumption that OS and TTD are equivalent between trial arms; this is uncertain due to the high degree of crossover from BAT to fedratinib in the BAT comparator arm
- The assumption that OS and TTD from FREEDOM-2 are generalisable to outcomes seen in NHS clinical practice, given that median treatment duration was lower in SACT and OS outcomes were more pessimistic.
- The assumption that patients who do not respond to fedratinib, or who stop responding to fedratinib, receive BAT that does not include suboptimal fedratinib.

1.3 The decision problem: summary of the EAG's key issues

The key issues related to the decision problem are described here, with other issues discussed in Section 2.3. It is noted that although the CS only presents evidence for fedratinib in the population previously treated with ruxolitinib, which is a subgroup of the population specified in the NICE scope, this is not considered a key issue as it is consistent with the use of fedratinib previously within the CDF.

Issue 1:No comparison against momelotinib

Report section	2.3.3
Description of issue and why the EAG has identified it as important	The CS does not provide a comparison against momelotinib, which was included as a comparator in the final NICE scope "*subject to NICE evaluation*" and has since received a positive recommendation (TA957). The company states that momelotinib has been excluded because it is not currently established in NHS clinical practice. It also argues that the overlap of the population eligible for momelotinib and the population eligible for fedratinib equates to a "*very small absolute number of patients*" due to momelotinib only being indicated in those with moderate to severe anaemia.
What alternative approach has the EAG suggested?	The EAG considers that a comparison against momelotinib should have been provided because it will be part of current practice in the time-period covered by the updated guidance on fedratinib. It notes that 67% of the fedratinib arm and 61% of the BAT arm in FREEDOM-2 had a haemoglobin ≤10g/dL at baseline, which aligns with the National Cancer Institute definition of moderate to severe anaemia. Therefore, the EAG does not agree with the company's argument that there will be low overlap between the population eligible for fedratinib and the population eligible for momelotinib.
What is the expected effect on the cost-effectiveness estimates?	The cost-effectiveness of fedratinib versus momelotinib in the subgroup of patients with moderate to severe anaemia is unknown at this time. Although the comparison of fedratinib versus BAT which is presented in the CS could be interpreted as being a relevant comparison for the subgroup without moderate to severe anaemia, it is possible that patients in both arms could potentially switch to momelotinib if they develop moderate to severe anaemia on either fedratinib or BAT. However, this possibility is not accounted for in the company's model. Therefore, the impact of momelotinib being available under TA957 is also unknown for the comparison of fedratinib versus BAT in patients who do not have moderate to severe anaemia when starting treatment.
What additional evidence or analyses might help to resolve this key issue?	The company could provide an economic model which includes momelotinib as a comparator treatment in the subgroup with moderate to severe anaemia. It could also provide an analysis of fedratinib versus BAT in the subgroup without moderate to severe anaemia. The

	structure of this model could be updated to account for the possibility of patients developing moderate to severe anaemia and switching to momelotinib after starting treatment with either fedratinib or BAT.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

The EAG identified one key issue related to the clinical effectiveness evidence that could impact on decision making. This is related to the design of the FREEDOM-2 study which allowed patients in the BAT arm to receive fedratinib treatment after completing the efficacy assessment at 6 months, or before then if they experienced disease progression. The impact of this treatment crossover on the cost-effectiveness estimates is further discussed in Section 1.5 (Issue 7).

Another issue related to the generalisability of the TTD and OS estimates from FREEDOM-2 to patients receiving fedratinib in clinical practice is discussed later in Section 1.5 (Issue 8), as it mainly concerns the potential overestimation of TTD and OS within the cost-effectiveness model.

Issue 2: The high proportion of patients crossing over from BAT to fedratinib in the comparator arm of FREEDOM-2 makes it difficult to compare outcomes beyond 6 months

Report section	3.2.3 & 3.3.9
Description of issue and why the EAG has identified it as important	There was a high proportion of crossover (69%) from BAT to fedratinib in the BAT arm of FREEDOM-2. The majority of this crossover (93%) occurred upon completion of the 6-month efficacy assessments and patients did not need to have progressed on BAT to cross over to fedratinib. This makes it difficult to compare OS, TTD or durability of response beyond 6 months using data from FREEDOM-2. The company attempted to use formal methods to adjust for treatment switching in the analysis of OS. However, it concluded that none of the methods explored were appropriate.
What alternative approach has the EAG suggested?	The EAG agrees that none of the formal methods to adjust for treatment switching explored by the company were appropriate. However, it notes that the OS and TTD curves fitted to the BAT arm and applied in the cost-effectiveness analysis include outcomes for patients who crossed over to fedratinib as data for these patients were not censored at crossover, and crossover to fedratinib was not considered to be a treatment discontinuation event.
What is the expected effect on the cost-effectiveness estimates?	The potential impact of this on the cost-effectiveness estimates is discussed further in Issue 7.
What additional evidence or analyses might help to resolve this key issue?	The EAG cannot recommend any additional analyses that might address this issue as it is mainly resulting from the design of the FREEDOM-2 study which fails to provide a randomised comparison beyond 6 months.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

The key issues related to the cost-effectiveness evidence are summarised in this section, with a focus on those issues that are most likely to affect decision making. In addition to these key issues, the EAG also identified and corrected some errors in the model which are not described in detail here (see Section 4.3.3.1). The EAG also preferred to incorporate updated drug acquisition costs (see Section 4.3.3.1), update the composition of BAT to reflect all drug treatments (see Section 4.4.3.8), and to adjust the estimates of RBC transfusions (see Section 4.3.3.10), but these all had a minor impact on the cost-effectiveness estimates, so are not considered key issues. It also identified some additional areas of uncertainty which were explored in scenario analysis but did not have a large impact on the ICER (see Sections 4.3.3.11, 4.3.3.13 and 4.3.3.14), and some concerns for which scenario analyses could not be conducted, but which were not considered key issues (Section 4.3.3.9 & 4.3.3.12).

Issue 3: Uncertainty regarding the composition of BAT received after fedratinib

Report section	4.3.3.2
Description of issue and why the EAG has identified it as important	The company's model assumes that patients who do not respond to fedratinib, or who respond initially but then stop responding, will not receive any subsequent treatment with fedratinib. This contrasts with the assumption that 77.6% of patients in the BAT arm will continue receiving suboptimal ruxolitinib, despite the population of FREEDOM-2 being patients who have previously relapsed on or failed to respond to ruxolitinib.
What alternative approach has the EAG suggested?	The EAG prefers to assume that the same proportion of patients will have suboptimal fedratinib as part of BAT after fedratinib as the proportion receiving suboptimal ruxolitinib as BAT after ruxolitinib (77.6% for both). To implement this the EAG also set the proportion receiving BAT to 100% for both responders and non-responders (i.e., 0% transition directly to supportive care). It believes this approach to be consistent with the committee's preference in TA756.
What is the expected effect on the cost-effectiveness estimates?	The impact of applying this change to the company's base-case was to reduce the size of the cost saving (-£[redacted] to -£[redacted] and increase the size of the QALY gain ([redacted] to [redacted]).
What additional evidence or analyses might help to resolve this key issue?	The EAG is not aware of any additional analyses or evidence that would resolve this issue.

Issue 4: Uncertainty regarding the proportion of patients transitioning straight to supportive care after fedratinib

Report section	4.3.3.3
Description of issue and why the EAG has identified it as important	The company's model assumes that 100% of patients stopping treatment with BAT, including those having suboptimal ruxolitinib, will transition directly to supportive care. This means patients who discontinue suboptimal ruxolitinib in the BAT comparator arm are not allowed to have other forms of BAT before transitioning to supportive care. This contrasts with the assumption in the fedratinib arm, whereby 66.7% of non-responders and 33.3.% of responders transition directly to supportive care and the remainder receive BAT. This means that supportive care is delayed in non-responders to fedratinib relative to non-responders to ruxolitinib, which is potentially favourable as supportive care is associated with a decline in utility values.
What alternative approach has the EAG suggested?	The EAG would prefer to adapt the model to assume that those patients receiving ruxolitinib as part of BAT are able to receive non-JAK inhibitor forms of BAT before transitioning to supportive care. However, as this was not possible within the current model structure, the EAG tested the impact of this potentially favourable model assumption by conducting an analysis assuming that 100% of patients stopping treatment with fedratinib transition directly to supportive care, bringing the modelling of fedratinib in line with the modelling of BAT. It should be noted that there is zero usage of BAT after fedratinib in this scenario and therefore zero usage of suboptimal fedratinib.
What is the expected effect on the cost-effectiveness estimates?	The EAG's scenario analysis increased the cost savings (-£[redacted] to -£[redacted]), but reduced the QALY gains ([redacted] to [redacted]) for fedratinib relative to BAT. This suggest that this assumption has an important impact on the cost-effectiveness estimates as approximately 17% of the QALY gains appear to be derived from this delay in the transition to supportive care in the fedratinib arm. The EAG has not applied this assumption in its base-case because this inconsistency is resolved when implementing the EAG's preference for allowing patients to have suboptimal fedratinib as part of BAT after fedratinib (see Issue 3). However, the EAG has explored the impact of assuming that 100% of fedratinib patients transition directly to supportive care and 0% receive BAT after fedratinib as a scenario including its other base-case assumptions as the starting point. In this scenario the treatment received after fedratinib is equivalent to the treatment received after suboptimal ruxolitinib in comparator arm BAT. This reduced the QALY gain from [redacted] to [redacted] and reduced the incremental costs to the extent that fedratinib became dominant. This is because this scenario excludes the cost BAT after fedratinib, including the suboptimal fedratinib included in the EAG's preferred base-case scenario.

What additional evidence or analyses might help to resolve this key issue?	The EAG would like to see the company's model adapted to differentiate between patients receiving JAK inhibitors as BAT and those receiving other forms of BAT, so that consistent assumptions can be applied to patients discontinuing both fedratinib and ruxolitinib. However, this adaptation is less necessary in scenarios that allow for suboptimal fedratinib as part of BAT after fedratinib.

Issue 5: Inconsistent assumptions regarding utility gains in non-responders to fedratinib and BAT

Report section	4.3.3.4
Description of issue and why the EAG has identified it as important	The company has estimated the gains in utility from baseline in responders and non-responders using a regression analysis that uses data pooled across both treatment arms and does not include a covariate for treatment allocation, but does include a covariate for response to treatment. It has then applied the utility gain for non-responders derived from this regression to the fedratinib arm but not to the BAT arm of the economic model.
What alternative approach has the EAG suggested?	The EAG prefers to apply the utility gain from baseline in non-responders estimated from the regression analysis equally to both arms.
What is the expected effect on the cost-effectiveness estimates?	Applying this single change to the company's base-case decreases the QALY gain ([redacted] to [redacted]) but has no impact on the incremental costs.
What additional evidence or analyses might help to resolve this key issue?	The company could provide a regression analysis which includes a covariate for treatment arm; however, care would need to be taken to properly handle patients crossing over from BAT to fedratinib.

Issue 6: Costing of ruxolitinib assumes high wastage due to dose changes

Report section	4.3.3.5
Description of issue and why the EAG has identified it as important	The mean daily dose of ruxolitinib received in the BAT arm of the FREEDOM-2 trial was 24.1 mg. However, the mean cost included in the model is equivalent to the cost for a daily dose of [redacted] mg. This is because multiple doses are recorded per cycle in FREEDOM-2 and the company's approach assumes that a new pack, sufficient for one cycle of treatment is dispensed at the start of the cycle, and then each time a dose modification is made within a cycle, any old packs are discarded and a whole new pack, sufficient for a whole cycle of treatment, is then dispensed. The EAG does not consider that this is likely to reflect how dose modifications are manged within the NHS. In addition, the EAG considers that the frequency of dose modifications within the trial may be higher than in clinical practice due to the requirement for more intensive adverse event monitoring in a trial setting. The EAG expects that if patients are having frequent haematological tests to determine the need for dose adjustments in clinical practice,

	then the medication dispensed would be adjusted accordingly to avoid the excessive wastage assumed by the company. Therefore, it considers that the company's approach is likely to have overestimated the cost of ruxolitinib.
What alternative approach has the EAG suggested?	The EAG prefers to apply the average initial dose distribution across the first 6 cycles in its base-case, with an assumption of 5% wastage for dose adjustments.
What is the expected effect on the cost-effectiveness estimates?	Applying the EAG's preferred approach to the company's base-case results in a decrease in the cost savings for fedratinib versus BAT (-£[redacted] to -£[redacted]), but fedratinib continues to dominate BAT (i.e. has lower costs and higher QALYs).
What additional evidence or analyses might help to resolve this key issue?	The company could provide an analysis of the time spent on each ruxolitinib dose which would remove the requirement to assume that a full pack providing 28 days of medication is dispensed each time the dose is changed and at the start of each cycle.

Issue 7: Uncertainty regarding duration of suboptimal ruxolitinib within BAT

Report section	4.3.4.6
Description of issue and why the EAG has identified it as important	The company has fitted parametric curves for TTD to Kaplan-Meier curves that include time on treatment with fedratinib in patients who crossed over from BAT to fedratinib. It is unclear whether these patients would have persisted with treatment for the same amount of time if fedratinib had not been available. Therefore, the TTD curves applied in the company's base-case potentially overestimate the expected time on treatment with BAT. It is also unclear whether OS would be similar if those patients had not switched to fedratinib (see Issue 2).
What alternative approach has the EAG suggested?	The company has explored the impact of using TTD and OS curves fitted to the patients in the BAT arm who did not crossover to fedratinib. The EAG considers that these represents a plausible alternative estimate of TTD and OS for BAT, although these estimates are also uncertain because of the small numbers of patients who did not crossover and the fact that these patients may be a selected group. It does not consider that this approach is preferable to the company's base-case analysis, but considers that this scenario analysis demonstrates the uncertainty in the company's cost-effectiveness estimates that exists due to using TTD and OS estimates that are not adjusted for crossover.
What is the expected effect on the cost-effectiveness estimates?	The company's scenario analysis using the BAT arm excluding crossovers (Scenario 7) had a large impact on the cost-effectiveness estimates, providing an ICER of £[redacted] per QALY for fedratinib versus BAT (£[redacted] when replicated by the EAG). This contrasts with the company's base-case in which fedratinib dominates BAT (i.e., has lower cost and higher QALYs). Applying the BAT arm TTD and OS curves excluding crossover patients to the EAG's preferred base-case increased

	both incremental costs and incremental QALYs, but the ICER reduced from £[redacted] per QALY to £[redacted] per QALY.
What additional evidence or analyses might help to resolve this key issue?	The EAG cannot recommend any additional analyses that might address this issue as it is mainly resulting from the design of the FREEDOM-2 study which fails to provide a randomised comparison beyond 6 months. The company has already explored formal methods to adjust for treatment switching and these were considered inappropriate by both the company and the EAG (see Issue 2).

Issue 8: Estimates of OS and TTD from FREEDOM-2 may overestimate the time on treatment and OS expected in clinical practice

Report section	4.3.3.7 (with clinical data discussed in 3.2.7, 3.3.4, 3.3.6, 3.3.8)
Description of issue and why the EAG has identified it as important	TTD and OS were both shorter for patients receiving fedratinib in SACT, compared to estimates from the FREEDOM-2 trial. Although the company provides some potential reasons for these differences, many of these relate to the characteristics of population treated. The EAG is concerned that this indicates that the outcomes from FREEDOM-2 may not be generalisable to the population who would receive fedratinib in clinical practice, which should be closely aligned to the population described in SACT.
What alternative approach has the EAG suggested?	The company has provided a scenario analysis in which the OS and TTD data from SACT are applied in the model instead of the data from FREEDOM-2. This is possible because the company's base-case already assumes no difference between the fedratinib and BAT trial arms and therefore the SACT data can be applied to both treatment arms. The EAG considers that this provides a plausible alternative estimate of expected TTD and OS in current practice.
What is the expected effect on the cost-effectiveness estimates?	Applying the SACT TTD and OS estimates to the company's base-case reduces the cost savings (-£[redacted] to -£[redacted]) and the QALY gains ([redacted] to [redacted]) for fedratinib versus BAT, but fedratinib continues to dominate BAT. Applying the SACT TTD and OS estimates to the EAG's preferred base-case reduced both incremental costs and incremental QALYs, but the ICER increased from £[redacted] per QALY to £[redacted] per QALY.
What additional evidence or analyses might help to resolve this key issue?	The EAG cannot suggest any additional analyses that might resolve this issue, but provides the scenario analysis results using the SACT data for the committee to consider.

1.6 Summary of EAG's preferred assumptions and resulting ICER

An indication of the impact of making individual changes to the company's base-case is provided in Section 4.4.3.1. These results are summarised in Table 2, along with the results for the EAG's preferred base-case scenario, and results for those scenario analyses that had a large impact on the cost-effectiveness estimates (see Section 4.4.3.2). Fedratinib dominated BAT (i.e., had lower costs and higher QALYs) in the company's base-case, but it had both higher costs and higher QALYs in some of the scenarios presented by the EAG. This makes the interpretation of changes in ICERs between scenarios more difficult. Therefore, the EAG has presented the incremental net monetary benefit (INMB) for each analysis and has used the change in INMB to present the magnitude of change from the company's base-case in Table 2.

The results presented in Table 2 demonstrate that the assumptions made in the costing of ruxolitinib, and the proportion of patients assumed to receive suboptimal fedratinib, are the key differences between the company and the EAG's preferred base-case scenarios. Fedratinib no longer dominates BAT in the EAG's preferred base-case, and the EAG's estimate of the ICER is above £30,000 per QALY. Whilst the EAG's preferred base-case scenario has an ICER of £[redacted] per QALY (£[redacted] for the probabilistic analysis), ICERs ranging from £[redacted] to £[redacted] are achieved when exploring alternative methods to extrapolate TTD and OS. These scenario analyses demonstrate that there is substantial decision uncertainty that arises from, a) the high proportion of patients in the BAT arm crossing over to receive fedratinib, and b) concerns regarding the generalisability of the data from FREEOM-2 due to the shorter TTD and OS observed in the SACT. In addition, fedratinib dominates BAT in the scenario analysis in which all patients stopping fedratinib are assumed to transition directly to supportive care without receiving subsequent BAT treatments. This demonstrates that there is significant decision uncertainty associated with the subsequent treatments received after fedratinib.

Table 2: EAG exploratory analyses and scenario analyses

Scenario	Incr. cost vs BAT	Incr. QALYs vs BAT	INMB at £20,000 threshold (Δ from company base-case)	ICER[a]
Company's base-case	[redacted]	[redacted]	[redacted]	Dominant
EAG EA 1: Correcting programming and implementation errors in the company's economic model and updated drug acquisition costs	[redacted]	[redacted]	[redacted]	Dominant
EAG EA 2: Proportion receiving suboptimal fedratinib after fedratinib is equal to proportion receiving	[redacted]	[redacted]	[redacted]	Dominant

Scenario	Incr. cost vs BAT	Incr. QALYs vs BAT	INMB at £20,000 threshold (Δ from company base-case)	ICER[a]
suboptimal ruxolitinib in the BAT comparator arm				
EAG EA 3: Utility gain for non-responders to BAT equal to utility gain for non-responders to fedratinib	[redacted]	[redacted]	[redacted]	Dominant
EAG EA 4: Ruxolitinib costing based on average initial dose distribution across the first 6 cycles in FREEDOM-2 plus 5% wastage for dose adjustments	[redacted]	[redacted]	[redacted]	Dominant
EAG EA 5: BAT comparator arm includes all drug treatments received within FREEDOM-2 (with the exclusion of RBC transfusions)	[redacted]	[redacted]	[redacted]	Dominant
EAG EA 6: RBC transfusion rate assumed equal between fedratinib and BAT	[redacted]	[redacted]	[redacted]	Dominant
EAG EA 7: Assuming all patients on fedratinib transition to supportive care after discontinuation	[redacted]	[redacted]	[redacted]	Dominant
EAG base-case: EAG EAs 1 to 6 – deterministic	[redacted]	[redacted]	[redacted]	[redacted]
EAG base-case: EAG EAs 1 to 6 – probabilistic	[redacted]	[redacted]	[redacted]	[redacted]
EAG SA1: Assuming all patients on fedratinib transition to supportive care after discontinuation	[redacted]	[redacted]	[redacted]	Dominant
EAG SA2: Using OS and TTD data in the BAT arm only from patients who did not crossover to fedratinib as with company's scenario 7	[redacted]	[redacted]	[redacted]	[redacted]
EAG SA3: Using OS and TTD data from SACT as with company's scenario in response to clarification question B8	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BAT - best available therapy; EAG external assessment group; EA - exploratory analysis; OS – overall survival; ICER - incremental cost-effectiveness ratio; INMB - incremental net monetary benefit; QALYs- quality-adjusted life-years; RBC - red blood cells; SA – scenario analysis; SACT – systemic anti-cancer therapy TTD – time to treatment discontinuation.

[a] *Dominant indicates that fedratinib has lower costs and higher QALY gains*

Modelling errors identified and corrected by the EAG are described in Section 4.3.3.1. For further details of the exploratory and scenario analyses done by the EAG, see Section 4.4.2 and Section 4.4.3.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

Overall, the External Assessment Group (EAG) considers the company's description of the underlying health problem in the company submission (CS) to be broadly appropriate, and a brief summary of the underlying health problem is provided here for context.

Myelofibrosis is a rare haematological disorder characterised by fibrosis (scarring) of the bone marrow.[1] As the bone marrow becomes more scarred, this can result in low numbers of circulating blood cells (cytopenia) and increased blood cell production outside of the bone marrow (extramedullary haematopoiesis), typically in the spleen or liver, which causes these organs to become enlarged.[1] Enlargement of the spleen (splenomegaly) causes abdominal pain/discomfort and early satiety (feeling full after eating a small amount of food).[2] Symptoms such as fatigue, breathlessness and bone pain are associated with low circulating levels of red blood cells (anaemia), while low levels of white blood cells (neutropenia) and platelets (thrombocytopenia) are associated with an increased risk of infections and bleeding, respectively.[1] In addition, patients can experience itch (pruritus) and constitutional symptoms, such as weight loss, night sweats and fever.[2]

Myelofibrosis may be primary (known as chronic idiopathic myelofibrosis) or it can occur as a consequence of polycythaemia vera or essential thrombocythaemia,[1] which are themselves both rare types of blood cancer.[3, 4] To predict prognosis and help guide treatment decisions, patients with myelofibrosis are classified into one of four risk categories (low, intermediate-1, intermediate-2 and high risk).[1] This can be done at diagnosis, using the original International Prognostic Scoring System (IPSS), or at any time, using either the Dynamic International Prognostic Scoring System (DIPSS) or the DIPSS Plus, which are adaptations of the IPSS for use throughout the disease course.[2, 5] The CS states that patients with intermediate-2 or high risk myelofibrosis have poor overall prognosis and very limited survival time.[2] The British Society for Haematology (BSH) guideline for the diagnosis and evaluation of prognosis of myelofibrosis reports median survival as being 4 years and 1.4 years in patients with an intermeidate-2 or high risk DIPSS classification, respectively.[5] The CS describes lower survival for patients in these risk groups who subsequently relapse or become refractory to existing treatments, reporting a median survival of 13-16 months for patients who have discontinued ruxolitinib treatment.[2] Patients with myelofibrosis are also at risk of their disease transforming to acute myeloid leukaemia (AML).[1] The CS states that 10 to 20% of people with primary myelofibrosis will progress to AML.[2]

Myelofibrosis has a low incidence of 0.6 per 100,000 people in the UK and represents 1% of all haematological malignancies.[6] The CS states that it typically occurs in older people and reports a

median age at diagnosis of 65 years.[2] However, the EAG notes that none of the sources cited in the CS for this estimate are UK sources and the median age provided by the Haematological Malignancy Research Network (HMRN) is 73 years.[6] The CS states that the total prevalent population of people with myelofibrosis in the UK is 2,130, which is based on an estimate from the HMRN.[6] It goes on to state that half of these people are expected to have intermediate-2 or high-risk disease. The EAG was unable to identify a source for this proportion from within the cited document, which was the TA386 guidance (Ruxolitinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis).[7] However, the company's budget impact model included as estimate of 49% of patients having intermediate-2 or high-risk disease at diagnosis, with the source quoted in the model being the cohort used to derive the IPSS.[8]

2.2 Critique of company's overview of current service provision

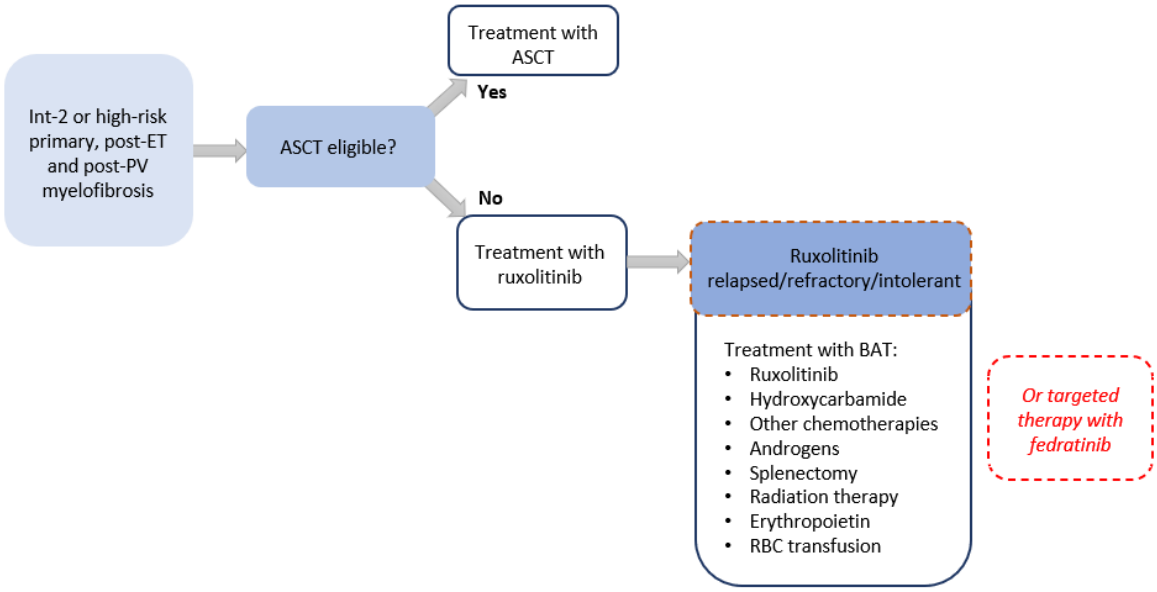
The company's presentation of the current pathway of care for people with intermediate-2 and high-risk myelofibrosis is summarised in Figure 1. The company notes that only a small minority of patients (5% to 10%) are eligible for potentially curative treatment with allogeneic stem cell transplantation (ASCT).[2] In those patients who are not eligible for ASCT, the company describes first-line treatment as targeted therapy with oral Janus associated kinase (JAK) inhibitors, such as ruxolitinib.

The company's proposed positioning of fedratinib is for patients who have been previously treated with ruxolitinib, which is consistent with the previous recommendation in TA756 (Fedratinib for treating disease-related splenomegaly or symptoms in myelofibrosis), which made fedratinib available within the Cancer Drugs Fund (CDF).[9] In the absence of fedratinib, second-line therapy is described as composing of largely supportive treatment options which it classifies as 'best available therapy (BAT).' The company describes BAT as including hydroxycarbamide, other chemotherapies, androgens, splenectomy, radiation therapy, erythropoietin, and red blood cell (RBC) transfusion. In addition to these supportive BAT options, the CS states that it is common for patients who are refractory to ruxolitinib or who relapse on ruxolitinib treatment, to continue to receive ruxolitinib, which is described in the CS as 'suboptimal' ruxolitinib treatment.[2] One of the reasons given for this continued use of suboptimal ruxolitinib, is the lack of alternative disease modifying therapies available, but another is that withdrawal of ruxolitinib can lead to an acute relapse of disease symptoms and occasionally haemodynamic decompensation, resulting in a "*septic shock-like syndrome.*" For these reasons, the BSH guideline recommends that ruxolitinib should not be stopped abruptly and that care should be taken to avoid a withdrawal reaction if patients transition from ruxolitinib to fedratinib.[10]

The CS states, "*Ruxolitinib is the only targeted treatment recommended for use in people with myelofibrosis (with intermediate-2 and high-risk disease) in clinical practice in the UK.*"[2] This was technically accurate at the time of the CS in March 2024, as NICE guidance on momelotinib (TA957:

Momelotinib for treating myelofibrosis-related splenomegaly or symptoms)[11] had not yet been published, although momelotinib received authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA) in January 2024 and positive Final Draft Guidance was published by NICE in February 2024.[12, 13] The EAG would argue that the company's description of the clinical pathway should have included momelotinib as it was a licensed treatment option for myelofibrosis patients (with moderate to severe anaemia) at the time of the CS. The relevance of momelotinib as a comparator is further discussed in Section 2.3.3.

Figure 1: Clinical pathway of care for people with intermediate-2 and high-risk myelofibrosis in England (reproduced from CS, Figure 3)



Abbreviations: ASCT - allogenic stem cell transplant; BAT - best available therapy; ET - essential thrombocythaemia; Int - intermediate; PV - polycythaemia vera; RBC - red blood cell.

2.3 Critique of company's definition of the decision problem

2.3.1 Population

The population addressed in the CS is "*adults with disease-related splenomegaly or symptoms of primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis who have been treated with ruxolitinib,*" (CS, Table 1).[2] The CS notes that this is narrower than the population covered by the marketing authorisation for fedratinib,[2] whose wording covers those who are JAK inhibitor naïve in addition to those who have been previously treated with ruxolitinib.[14] However, the company argues that this restriction is appropriate because this targets fedratinib treatment in the population for whom it provides the most clinical benefit and cost-effectiveness and this was the group recommended for treatment in TA756.[2] As treatment with ruxolitinib is recommended only for patients with intermediate-2 or high-risk disease,[7] the company's proposed target population is effectively also restricted to those with intermediate-2 or high-risk disease (CS, Figure 3).[2] However,

this restriction is consistent with the eligible population specified in the CDF managed access agreement for TA756,[15] and the population recruited to the FREEDOM-2 clinical trial (the main trial informing the CS, which compared fedratinib to BAT).[16] Overall, the EAG is satisfied that the population specified in the CS is a well-defined subgroup of the marketing authorisation and there is a clear rationale for focusing on this group. However, the EAG notes that the company's choice to focus on a narrower population means that no evidence is provided for patients who are JAK inhibitor naïve or who have low or intermediate-1 risk disease. The population addressed in the CS is therefore narrower than that specified in the NICE scope, which does not restrict according to treatments received previously or the patient's risk categorisation.[1]

2.3.2 Intervention

The intervention evaluated in the CS is fedratinib (Inrebic®, Bristol Myers Squibb [BMS]), an oral JAK inhibitor.[2] Fedratinib selectively inhibits JAK2, with higher inhibitory activity for JAK2 over family members JAK1, JAK3, and tyrosine kinase 2 (TYK2).[2] Fedratinib has a UK marketing authorisation for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis who are JAK inhibitor naïve or have been treated with ruxolitinib.[14] The recommended dose is 400 mg once daily and treatment can be continued for "*as long as patients derive clinical benefit.*"[14] Dose modifications should be considered for managing haematological and non-haematological toxicities but treatment should be discontinued in those who cannot tolerate a dose of 200 mg daily.[14] Dose reductions are recommended for patients with severe renal impairment and use should be avoided in those with severe hepatic impairment.[14] The summary of product characteristics (SPC) does not specify that patients should discontinue if disease progression occurs,[14] but patients were required to discontinue fedratinib treatment on disease-progression in FREEDOM-2 (see Section 3.2.3). The managed access agreement for use of fedratinib in the CDF under TA756 states it can be continued, "*until loss of clinical benefit or unacceptable toxicity or patient choice to stop treatment*."[15]

Recognised adverse events (AEs) occurring very commonly include gastrointestinal disorders (e.g., nausea, vomiting, diarrhoea and constipation), urinary tract infections, fatigue or weakness, headache, muscle spasms, bleeding, and abnormalities in blood test results (e.g., anaemia, thrombocytopenia, neutropenia, and elevations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), amylase/lipase, creatinine).[14] Treatment initiation is not recommended in, "*patients with a baseline platelet count below 50 x 10^9/L and ANC [absolute neutrophil count] < 1.0 x 10^9/L.*"[14] Cases of Wernicke's encephalopathy have been reported in patients taking fedratinib and thiamine levels should be assessed before starting treatment and monitored periodically thereafter (e.g., each month for the first 3 months and every 3 months thereafter) and as clinically indicated.[14] Fedratinib treatment should not be started in patients with thiamine deficiency.[14]

Fedratinib is administered orally as a single daily dose of 400 mg (four 100 mg tablets) taken with or without food.[2] The list price for fedratinib is £6,119.68 for 120 capsules, A confidential simple discount Patient Access Scheme (PAS) agreement is in place (see Section 4.2.5.5.1) and all cost-effectiveness results presented in the CS and the EAG report use the PAS price.[2] The cost-effectiveness results when using confidential comparator prices are included in a separate confidential appendix.

2.3.3 Comparators

The comparators defined in the NICE scope for the population with previous ruxolitinib treatment are[1]:

- established clinical practice (including but not limited to hydroxycarbamide, other chemotherapies, androgens, splenectomy, radiation therapy, erythropoietin and RBC transfusion)
- momelotinib

Momelotinib was included in the scope "*subject to NICE evaluation*",[1] but has since been recommended in TA957 for the subgroup of patients with moderate to severe anaemia.[11] The CS does not provide any comparison against momelotinib because the company argues that it is not currently established in NHS clinical practice.[2] However, the EAG considers that a comparison against momelotinib should have been provided because it will be part of current practice in the time period covered by the updated guidance on fedratinib.

In response to the clarification request (clarification response, question A1),[17] the company stated that the potential future overlap of the population eligible for momelotinib and the population eligible for fedratinib equates to a "*very small absolute number of patients*" due to momelotinib only being indicated in those with moderate to severe anaemia. However, the company did not provide any quantitative assessment of the proportion of the target population who are likely to have moderate to severe anaemia as requested (clarification response, question B4).[17] The EAG notes that according to the subgroup analysis of FREEDOM-2 on baseline haemoglobin provided in the CS, Figure 35, 67% of the fedratinib arm (90/134) and 61% of the BAT arm (41/67) had a baseline haemoglobin (Hb) ≤10g/dL.[2] In TA957, the committee considered analyses using two alternative definitions of moderate to severe anaemia (Hb ≤10g/dL and Hb ≤12g/dL),[11] but using even the more strict definition of Hb ≤10g/dL, which aligns with the National Cancer Institute definition of moderate to severe anaemia,[18] would mean that at least 60% of the population of the FREEDOM-2 study would have been classed as having moderate to severe anaemia at baseline. The EAG therefore believes that momelotinib is a relevant comparator for a substantial proportion of the population within the company's definition of the target population for fedratinib.

The CS defines established clinical practice in the population previously treated with ruxolitinib in the absence of fedratinib as being 'best available therapy' (BAT).[2] The company's description of BAT is consistent with the definition of established clinical practice in the NICE scope with the exception that the company has included ruxolitinib as an option within BAT, whereas the NICE scope only explicitly included ruxolitinib as a comparator for JAK inhibitor naïve patients. The use of 'suboptimal' ruxolitinib in patients whose disease does not respond to ruxolitinib or who have initially responded but then lost response to ruxolitinib has been previously described in TA756 as part of current clinical practice due to the limited effectiveness of the other BAT treatment options.[9] However, the EAG notes that at the time of TA756, fedratinib was the only alternative JAK inhibitor available. The EAG therefore agrees that suboptimal ruxolitinib is likely to be part of BAT in patients in whom there is no other alternative JAK inhibitor. However, it considers that the availability of momelotinib within TA957 is likely to reduce the proportion of patients receiving suboptimal ruxolitinib as those with moderate to severe anaemia would be eligible for treatment with momelotinib. Therefore, the EAG considers that BAT including suboptimal ruxolitinib, as presented in the CS, is only a relevant comparator in those not eligible to receive momelotinib under TA957.

2.3.4 Outcomes

The key clinical outcomes specified in the NICE scope are[1]:

- Spleen size
- Symptom relief (including itch, pain and fatigue)
- Overall survival (OS)
- Leukaemia-free survival
- Response rate
- Hematologic parameters (including RBC transfusion and blood count)
- Adverse effects of treatment
- Health-related quality of life (HRQoL).

The outcome of spleen size is addressed in the CS by various outcomes reported in FREEDOM-2. The primary outcome in FREEDOM-2 is the spleen volume response rate, defined as the proportion of patients with a spleen volume reduction (SVR) ≥ 35% assessed using either magnetic resonance imaging (MRI) or computer tomography (CT) scan by blinded central review. FREEDOM-2 also included secondary outcomes of SVR ≥ 25% assessed by MRI or CT scan and spleen response by palpation (≥ 50% reduction in spleen size if spleen was > 10 cm below left costal margin [LCM] or non-palpable if spleen was palpable at 5 to 10 cm below the LCM).

Symptom relief is addressed in the CS by the secondary outcome in FREEDOM-2 of symptom response rate defined as the proportion of patients with a ≥ 50% reduction in myelofibrosis-associated symptoms measured using the total symptom score (TSS) from the Myelofibrosis Symptom Assessment Form (MFSAF). Mean percent changes from baseline in MFSAF TSS scores over the trial period are also reported in the clinical study report (CSR) for FREEDOM-2 (CSR Figure 14.2.2.5),[19] but were not provided in the CS.[2] Individual components of the MFSAF (e.g., fatigue, night sweats, itching, pain / discomfort and early satiety) are reported in the FREEDOM-2 CSR, but are not summarised in the CS.[2, 19]

Response rate as a clinical effectiveness outcome is provided in CS Section B.2.6, using several different definitions of response (SVR ≥ 35%, MFSAF TSS reduction ≥ 50%, SVR ≥ 25% and spleen response by palpation)[2]. However, an additional definition of response based on spleen or symptom response (SVR ≥ 35% or MFSAF TSS reduction ≥ 50%) is employed in the economic model CS (CS, B.3.2.2.2).[2]

Overall survival (OS) is reported in the CS using data from both FREEDOM-2 and the Systemic Anti-Cancer Therapy (SACT) database, but leukaemia-free survival was not reported as it was not available from either FREEDOM-2 or SACT. Other time-to-event outcomes from FREEDOM-2 which are included in the CS, but which were not specified in the final NICE scope, are spleen and disease progression-free survival (SDPFS) and durability of response using various definitions of response (SVR ≥ 35%, MFSAF TSS reduction ≥ 50% and spleen response by palpation). Duration of treatment is also presented as an outcome from the SACT database and time to discontinuation data from FREEDOM-2 are presented in the CS as an input to the economic model (CS Section B.3.3.6.3).[2]

The remaining outcomes specified in the scope (haematological parameters, adverse effects of treatment and HRQoL) are addressed in the CS using data from FREEDOM-2. HRQoL outcomes are available in FREEDOM-2 from both the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 (EORTC QLQ-C30) and the EuroQol 5-dimensions - 5-level (EQ-5D-5L; both visual analogue scale [VAS] and utility index).[2] However, the EQ-5D-5L utility outcomes do not inform the economic modelling as the company instead calculates Myelofibrosis - 8-Dimension (MF-8D) utilities by combining outcomes from the EORTC QLQ-C30 and the MFSAF.

2.3.5 Other relevant factors

The company states that the conditions for applying a quality-adjusted life-year (QALY) weighting, on the basis of disease severity, are not met for this technology.

The final NICE scope did not identify any special considerations related to equity or equality, and none were identified in the CS.

Table 3: The decision problem (adapted from CS, Table 1)

	Final scope issued by NICE	Decision problem addressed in the CS and rationale if different from NICE scope	EAG comments
Population	Adults with disease-related splenomegaly or symptoms of: Primary myelofibrosis (also known as chronic idiopathic myelofibrosis) Post-polycythaemia vera myelofibrosis, or, Post-essential thrombocythaemia myelofibrosis	Adults with disease-related splenomegaly or symptoms of primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis who have been treated with ruxolitinib. This position is narrower than the marketing authorisation for fedratinib because the population of patients previously treated with ruxolitinib reflects where fedratinib provides the most clinical benefit and cost-effectiveness. This approach was accepted by NICE as appropriate during the original submission.	The EAG is satisfied with the company specifying a narrower population, and notes that this is consistent with the population who received fedratinib within the CDF under TA756 and the population of the FREEDOM-2 clinical trial. The EAG also notes that in both the CDF and the FREEDOM-2 trial, patients had to have had prior treatment with ruxolitinib and to have intermediate-2 or higher risk myelofibrosis.
Intervention	Fedratinib 400 mg	Fedratinib 400 mg	Not applicable

	Final scope issued by NICE	Decision problem addressed in the CS and rationale if different from NICE scope	EAG comments
Comparator(s)	For people whose disease was not previously treated with a JAK inhibitor: ruxolitinib momelotinib (subject to NICE evaluation) For people whose disease was previously treated with ruxolitinib or if ruxolitinib is not appropriate (including people with low or intermediate-1 risk disease): established clinical practice (including but not limited to hydroxycarbamide, other chemotherapies, androgens, splenectomy, radiation therapy, erythropoietin and RBC transfusion). momelotinib (subject to NICE evaluation)	For people whose disease was previously treatment with ruxolitinib or if ruxolitinib is not appropriate (including people with low or intermediate-1 risk disease) Established clinical practice, otherwise referred to as BAT (including but not limited to ruxolitinib, hydroxycarbamide, other chemotherapies, androgens, splenectomy, radiation therapy, erythropoietin, and RBC transfusion). This appraisal focuses on standard of care available in the UK (ruxolitinib or BAT). Momelotinib is currently subject to a NICE appraisal and is not currently established in NHS clinical practice (in England and Wales) and therefore cannot be viewed as a comparator in the evaluation of fedratinib	The company has included ruxolitinib as part of established clinical practice in the group previously treated with ruxolitinib, whereas it was not included within the description of established clinical practice for this group in the final NICE scope. However, the EAG considers this to be reasonable as continuing with 'sub-optimal' ruxolitinib has been considered part of established clinical practice in the absence of alternative treatments such as fedratinib and momelotinib. The EAG notes that since the final NICE scope for fedratinib was published, momelotinib has received a positive NICE recommendation in TA957,[11] and therefore it considers that momelotinib is a relevant comparator for those patients covered by the recommendation in TA957. It also notes that treatment with momelotinib is likely to replace suboptimal ruxolitinib in those patients eligible for treatment with momelotinib, i.e., those with moderate to severe anaemia.

	Final scope issued by NICE	Decision problem addressed in the CS and rationale if different from NICE scope	EAG comments
Outcomes	• Spleen size • Symptom relief (including itch, pain and fatigue) • OS • Leukaemia-free survival • Response rate • Hematologic parameters (including RBC transfusion and blood count) • AEs of treatment • HRQoL	• Primary outcome Percentage of patients with ≥ 35% SVR in the fedratinib and BAT arms • Key secondary outcomes Percentage of patients with at least 50% reduction in myelofibrosis-associated symptoms Percentage of patients with ≥ 25% SVR • Secondary outcomes Spleen response rate Durability of response Spleen and disease progression-free survival OS AEs of treatment HRQOL • Exploratory outcomes Haematological parameters (including RBC transfusion and blood count) Time to spleen response Best spleen volume response rate Neither FREEDOM-2 nor the SACT data reported leukaemia-free survival. FREEDOM-2 reported spleen and disease progression-free survival, which was defined as time from randomisation to death due to any reason or disease progression (modified IWG-MRT 2013 including ≥ 25% increase in spleen volume by MRI/CT scan). Therefore, leukaemia-free survival will not be reported	Overall, the EAG is satisfied that the CS covers the outcomes specified in the final NICE scope where these were available. The EAG notes that there were several definitions of response to treatment within FREEDOM-2 and the definition of response used in the model classified patients as responders if they had either a spleen response (≥ 35% SVR) or a symptom response (≥ 50% reduction in myelofibrosis-associated symptoms).

	Final scope issued by NICE	Decision problem addressed in the CS and rationale if different from NICE scope	EAG comments
Subgroups to be considered	• People whose disease was previously treated with a JAK inhibitor • Prognostic factors such as haemoglobin <10 g/dL, leukocyte count >25 x 109/L, circulating blasts (immature blood cells) ≥ 1%, presence of constitutional symptoms or platelet count	No subgroup analyses are planned. The company states that it is presenting the most relevant case as FREEDOM-2 was designed to align with the population of interest for this assessment. Myeloblasts ≥ 5% in peripheral blood was an exclusion criterion for FREEDOM-2.	The CS is already restricted to those patients with previous JAK inhibitor treatment. Subgroup results for the primary outcome from FREEDOM-2 are presented by baseline haemoglobin (≤10g/dL and > 10g/dL), white blood cell count at baseline (≥25 x 10^9/L and <25 x 10^9/L), blood blasts at baseline (≥1% and <1%), platelet count (50 to 100 and ≥100 x 10^9/L) presence of constitutional symptoms.
Special considerations including issues related to equity or equality	None identified	None identified (CS Section B.1.4)[2]	Not applicable.

Abbreviations: AEs, adverse effects; BAT, best available therapy; CDF, Cancer Drugs Fund; CT, computed tomography; HRQoL, health-related quality of life; IWG-MRT, International Working Group-Myeloproliferative Neoplasms Research and Treatment; JAK, Janus associated kinase; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OS, overall survival; PSS, Personal Social Services; RBC, red blood cell; SACT, Systemic Anti-Cancer Therapy; SVR, spleen volume reduction; MFSAF TSS, Myelofibrosis Symptom Assessment Form total symptom score; MRI, magnetic resonance imaging.

3 CLINICAL EFFECTIVENESS

The clinical evidence contained in the CS[2] is comprised of:

- A systematic literature review (SLR)
- Summary and results for two clinical studies of fedratinib.

This chapter summarises and critiques the company's review methods and clinical effectiveness data. Full details are presented in the CS Section B.2 and the CS Appendix D.[2]

3.1 Critique of the methods of review

3.1.1 Summary and critique of company SLR

CS Section B.2.1 and CS Appendix D.1 state that a systematic literature review (SLR) was conducted in February 2020 to identify randomised controlled trials (RCTs) and prospective non-RCTs of fedratinib and comparator therapies for myelofibrosis.[2] This SLR identified 247 studies from 453 publications; however, these are not described further in the CS. A subsequent (similar) search strategy document with a search date of April 2021 was submitted by the company with their clarification response,[17] but it was unclear whether these additional search results were screened by the company within an SLR, given that the CS only refers to a SLR conducted in February 2020.[2]

CS Section 2.1 lists five studies of fedratinib, either identified from the SLR or completed since the SLR (summarised in Table 4 below).[2] Of these, only the FREEDOM-2 RCT and the Systemic Anti-Cancer Therapy (SACT) dataset[20] are used in the CS, both of which were identified after the company's SLR. The CS states that no other pharmaceuticals have been approved by NICE for this indication since February 2020, and so no further evidence is anticipated to be found other than the pivotal trial FREEDOM-2 which provides head-to-head data of fedratinib vs. BAT; and that therefore an updated SLR is not required.[2] The company's clarification response (question A8) states that the company has monitored ongoing developments, and that no further trials of fedratinib or other relevant interventions for patients with intermediate-2 or high-risk myelofibrosis previously treated with ruxolitinib have been published since February 2020, other than FREEDOM-2.[17] The clarification response (question A8) also notes that momelotinib has recently been approved by NICE, but that the company does not consider this a relevant comparator.[17]

3.1.2 Critique of company searches

The search strategy for the SLR for clinical evidence is presented in CS Appendix D.[2] The search aimed to identify evidence related to treating patients with myelofibrosis (D.1.). The CS reports on an initial search that was performed in August 2018, with two later updates: one covering evidence published between August 2018 and October 2019, and one covering evidence from September 2019 to February 2020.[2] The clarification response provides details of a further update carried out in April 2021.[17]

However, with no update searches run since April 2021, there is still the potential for more recent evidence outside of the known trials (FREEDOM and FREEDOM-2, mentioned in Section D.1.) to have been missed.

As part of each search (the original in 2018 and the three later updates), the expected core bibliographic databases (MEDLINE, Embase and Cochrane Library) were searched systematically. Additionally, websites of relevant conference proceedings were checked for papers from the last two meetings. Once relevant SLR and meta-analysis publications had been identified, the reference lists of these sources were also checked, which did find additional eligible studies according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) diagram (CS Appendix D.1.3, Figure 1).[2] In terms of trial registers, a search of ClinicalTrials.gov was performed. However, as confirmed in the company's clarification response (question A3),[17] the World Health Organisation (WHO) International Clinical Trials Registry Platform was not searched in addition to this, which the EAG deems to be sub-optimal for ensuring a comprehensive strategy.

Search strategies for the original review and the two search updates are recorded in CS Appendix D (Tables 8-10),[2] although, regrettably, without the number of results for each line of each search. In the April 2021 search update provided as part of the company's clarification response, line-by-line result numbers are recorded. Since the Medline and Embase searches were performed on embase.com, the EAG has been unable to replicate these exactly.

The search strategies themselves have generally been logically devised and make use of both subject headings and free-text search terms. However, the same search string seems to have been used for Embase and Medline, without adapting the subject headings for the specialised Emtree and MeSH thesauri accordingly. Databases like Embase and Medline may have unique references that are not indexed in the other databases searched, which means that a search string that has not been adapted for the two different thesauri risks missing references.

A publication language limit of English-language-only has been applied, but this has not been explained or justified in the CS. The company's clarification response (question A5) highlights the wide use of English in academic publications and submissions to NICE.[17] However, the EAG would point out the risk of a potential language bias leading to some evidence being missed because it is published in another language or unfavoured by journals with a preference for publishing studies written in English.

Search terms based on existing search filters have been used to identify publications of the study types of interest without a citation given for the source of the filters or explanation of any adaptations made to them. The company's clarification response (question A4) indicates that these were adapted from

filters designed by the Scottish Intercollegiate Guidelines Network (SIGN), noting a history of SIGN collaborating with NICE.[17] The EAG recommends that filters are used in their full tried and tested form, for which they have been validated to work most effectively, to minimise the risk of missing potentially relevant evidence.

3.1.3 Critique of quality assessment

The CS (Section B.2.5.1) outlines processes undertaken to minimise bias in the FREEDOM-2 RCT, but does not assess risk of bias using a validated checklist.[2] The company's clarification response (question A15) states that a critical appraisal of this study has not been conducted by the company.[17]

3.1.4 Overall EAG view on company's systematic literature review methods

The EAG considers that the company should have presented an updated search and updated SLR for relevant studies, as well as a risk of bias assessment for included studies. However, the EAG agrees that the FREEDOM-2 head-to-head RCT is likely to be the most appropriate study for comparing fedratinib vs. BAT. The EAG notes that momelotinib is also a comparator in the NICE scope[1] and has recently been recommended by NICE. The company has not undertaken an updated SLR to identify studies of momelotinib and has not presented any comparison against momelotinib within the CS.

3.2 Characteristics of studies of fedratinib

3.2.1 Studies identified and listed in CS

CS Section 2.1 lists studies evaluating fedratinib (summarised in Table 4).[2] The CS presents data from two of these studies: the FREEDOM-2 RCT of fedratinib vs. BAT (included in the CS for clinical effectiveness and in the company's economic model), and the SACT dataset[20] of fedratinib in the CDF population (included in the CS for clinical effectiveness, but only included in the company's economic model in a scenario analysis). The additional studies from Table 4 are summarised in CS Appendix D.[2] The remainder of this EAG report focusses on FREEDOM-2 and the SACT dataset, as in the CS.

Table 4: Studies of fedratinib listed in CS

Study	Design	Line of therapy	Population	Intervention	Comparator	Used in CS	In company model
FREEDOM-2	RCT (Phase 3)	Previous ruxolitinib	Intermediate-2 or high risk myelofibrosis	Fedratinib	BAT	Yes	Yes
SACT dataset[20]	Real-world study in CDF population	Previous ruxolitinib	Intermediate-2 or high risk myelofibrosis	Fedratinib	-	Yes	Yes, after clarification (scenario only)
FREEDOM	Single-arm (Phase 3)	Previous ruxolitinib	Intermediate-2 or high risk myelofibrosis	Fedratinib	-	No	No

Study	Design	Line of therapy	Population	Intervention	Comparator	Used in CS	In company model
JAKARTA-2	Single-arm (Phase 2)	Previous ruxolitinib	Intermediate-1 with symptoms, intermediate-2 or high risk myelofibrosis	Fedratinib	-	No	No
JAKARTA	RCT (Phase 3)	Ruxolitinib -naïve	Intermediate-2 or high risk myelofibrosis	Fedratinib	Placebo	No	No

Abbreviations: BAT - best available therapy; CDF - Cancer Drugs Fund; CS - company submission; RCT - randomised controlled trial.

3.2.2 Ongoing studies

The CS (Section B.2.11) does not cite any other ongoing studies other than FREEDOM-2.[2]

3.2.3 Study design for fedratinib studies included in CS: FREEDOM-2 and SACT

An overview of FREEDOM-2 and the SACT dataset[20] are presented in Table 5, and further detail is provided in CS Section B.2.[2] This section summarises the design of the two studies and their consistency with the final NICE scope,[1] company decision problem and clinical practice.

Population: The FREEDOM-2 RCT enrolled 201 patients with intermediate-2 or high-risk myelofibrosis who had inadequate response or complications on previous ruxolitinib. The SACT dataset included 54 patients in the UK CDF population with similar characteristics to those in FREEDOM-2. The populations of FREEDOM-2 and SACT are consistent with the restricted population addressed in the CS, i.e., people with myelofibrosis who have had had prior ruxolitinib.

Intervention: Patients in FREEDOM-2 were randomised to fedratinib (N=134) or BAT (N=67) and could remain on treatment until disease progression (according to International Working Group-Myeloproliferative Neoplasms Research and Treatment [IWG-MRT]-2013 criteria) or unacceptable toxicity. In SACT, all N=54 patients received fedratinib and treatment in the CDF could be continued "*until loss of clinical benefit or unacceptable toxicity or patient choice to stop treatment.*" The intervention in FREEDOM-2 and SACT (i.e., fedratinib) is consistent with the final NICE scope[1] and the company decision problem.

Comparators: The comparator arm in FREEDOM-2 was BAT, which included a range of therapies listed in Table 6. Patients in the BAT arm could cross over from BAT to fedratinib after the end of cycle 6 (EOC6; at approximately 6 months), or earlier in the event of disease progression. As noted in Section 2.3.3 of this EAG report, the composition of the BAT arm appears consistent with the description of 'established clinical practice' in the NICE scope,[1] with the exception that 78% of patients in the BAT

arm received ruxolitinib. The EAG agrees that 'suboptimal' ruxolitinib is likely to be part of BAT, although, as noted in Section 2.3.3., availability of momelotinib may reduce the use of suboptimal ruxolitinib. In addition, as discussed in Section 2.3.3, the EAG considers momelotinib to be a relevant comparator (as per the NICE scope),[1] but the CS does not provide any evidence allowing a comparison of fedratinib versus momelotinib.

Outcomes: For FREEDOM-2, reported outcomes included the following (see Table 5 for details): spleen volume response rate at EOC6 (various definitions); symptom response rate at EOC6; durability of spleen and symptom response; time to spleen response; best spleen volume response; anaemia response; RBC transfusion dependency; spleen and disease progression-free survival (SDPFS); overall survival (OS); adverse effects (AEs); and health-related quality of life (HRQoL); while time to discontinuation (TTD) was reported in the cost-effectiveness section of the CS. For SACT,[20] reported outcomes included OS, treatment duration (equivalent to TTD), and reasons for discontinuation. Overall, the EAG is satisfied that the CS covers the outcomes specified in the NICE scope[1] where these were available. The EAG notes that since the majority (69%) of patients in the BAT arm of FREEDOM-2 crossed over to fedratinib, this study has limited ability to provide comparative data for fedratinib vs. BAT for time-to-event outcomes beyond EOC6 (i.e. beyond 6 months).

Data cut-offs and median follow-up: For FREEDOM-2, the data cut-off in the CS was December 2022.[2] The median follow-up time in FREEDOM-2 varied by outcome: median follow-up was 36 weeks (fedratinib) and 19 weeks (BAT) for durability of spleen volume response; 12 weeks (fedratinib) and 8 weeks (BAT) for durability of symptom response; 46 weeks (fedratinib) and 24 weeks (BAT) for SDPFS; and 64 weeks (fedratinib) and 64 weeks (BAT) for overall survival. The CS (Section B.2.11) states that FREEDOM-2 is ongoing but no longer recruiting and the estimated completion date is June 2025.[2] For SACT, the data cut-off in the SACT report[20] was 31 October 2022 and median follow-up was 4.6 months for treatment status and discontinuations. However, for OS in SACT, a reassessment of vital status was performed on 5 February 2024; the median follow-up time was then 15.5 months (471 days).[20]

Generalisability: The populations, interventions, comparators and outcomes for the two studies appear broadly relevant to the NICE scope[1] and the company decision problem.

Table 5: Design of fedratinib studies included in CS: FREEDOM-2 and SACT (adapted from CS Tables 3, 4, 5 and 10)

Study	FREEDOM-2 (NCT03952039)	SACT dataset
Study design	RCT (Phase 3, multicentre, open-label)	Real-world data collection in CDF population
Location	16 countries including UK	UK
Population	• Intermediate-2 or high-risk myelofibrosis and splenomegaly • Previous ruxolitinib • N=201	• Intermediate-2 or high-risk myelofibrosis and splenomegaly and/or symptoms • Previous ruxolitinib • N=54
Definition of inadequate response to ruxolitinib	• Previous ruxolitinib for ≥ 3 months with inadequate response as refractory or relapsed (< 10% SVR by MRI or < 30% decrease from baseline in spleen size by palpation or regrowth), or • Previous ruxolitinib for >28 days with a complication requiring RBC transfusion or grade ≥ 3 AEs of thrombocytopenia, anaemia, hematoma, and/or haemorrhage	•
Intervention(s)	• Fedratinib 400 mg in 4-week cycles (N=134) • Remain on fedratinib until disease progression or unacceptable toxicity	• Fedratinib 400 mg in 4-week cycles (N=54) • Remain on fedratinib until disease progression or unacceptable toxicity
Comparator(s)	• BAT (see Table 6; N=67) • Could cross over from BAT to fedratinib after EOC6, or earlier in event of disease progression	None
Used in marketing authorisation	No	No
Used in model	Yes	Yes, after clarification but only in a scenario analysis
Reported outcomes in NICE decision problem	• Spleen volume response rate: ○ ≥ 35% SVR via MRI/CT at EOC6 ○ ≥ 25% SVR via MRI/CT at EOC6 ○ Spleen response by palpation at EOC6 • Symptom response rate ○ ≥ 50% reduction in total symptom score (TSS) via MFSAF at EOC6 • Overall survival (OS) • Anaemia response (≥ 2 g/dL increase in haemoglobin in transfusion-independent participants, or transfusion-dependent participants who become transfusion independent) • RBC transfusion dependency • Adverse effects of treatment • Health-related quality of life	• Overall survival
Other reported outcomes	• Durability of spleen volume response • Durability of symptom response • Spleen and disease progression-free survival (SDPFS; time to death or disease progression as per modified IWG-MRT 2013 criteria including ≥25% increase in spleen volume by MRI/CT) • Time to spleen response • Best spleen volume response	• Treatment duration • Reasons for discontinuation
Data cut-off	• December 2022	• 31st October 2022 (treatment duration; discontinuations) • 5th February 2024 (overall survival)

Study	FREEDOM-2 (NCT03952039)	SACT dataset
Median follow-up	• Varies by outcome	• 4.6 months (treatment duration; discontinuations) • 15.5 months (overall survival)

Abbreviations: AE - adverse event; BAT - best available therapy; CDF - Cancer Drugs Fund; CT - computed tomography; EOC6 - end of cycle 6; MRI - magnetic resonance imaging; RBC - red blood cell; RCT - randomised controlled trial; SVR - spleen volume reduction.

3.2.4 Therapies received in BAT arm of FREEDOM-2

Treatments received in the BAT arm of FREEDOM-2 are shown in Table 6 (clarification response, question A12).[17] Patients could receive more than one BAT treatment sequentially or in combination. The most common treatments were ruxolitinib (78%), RBC transfusion (28%) and hydroxyurea (18%).

Table 6: FREEDOM-2: BAT therapies received (adapted from company's clarification response Table 1)

Treatment[a]	BAT (N = 67)
Ruxolitinib	52 (78)
RBC Transfusion	19 (28)
Hydroxyurea	12 (18)
No Treatment	2 (3)
Danazol	1 (1.5)
Hydroxycarbamide	1 (1.5)
Interferon	1 (1.5)
Mercaptopurine	1 (1.5)
Methylprednisolone	1 (1.5)
Prednisolone	1 (1.5)
Prednisone	1 (1.5)
Thalidomide	1 (1.5)

[a] *A participant may be counted in multiple lines, if more than 1 option was taken as BAT.*

3.2.5 Analysis populations and crossover status in FREEDOM-2 and SACT

Analysis populations are shown in

Table 7. In FREEDOM-2, as noted earlier, patients in the BAT arm could cross over from BAT to fedratinib after EOC6, or earlier in the event of disease progression. In total, 46 (69%) of BAT participants crossed over; 43 crossed over at EOC6 and 3 patients crossed over earlier upon progression. In SACT, 54 patients were analysed.[20]

Table 7: Analysis populations and crossover (adapted from CS Table 8)

	FREEDOM-2		SACT
Analysis population	**Fedratinib (n = 134)**	**BAT (n = 67)**	**Fedratinib (N=54)**
Intention to treat (ITT) population[a]	134 (100%)	67 (100%)	54 (100%)
Safety population[b]	134 (100%)	67 (100%)	-
Crossover efficacy population[c]	-	46 (69%) (43 at EOC6, 3 earlier on progression)	-

Abbreviations: BAT - best available therapy; EOC6 - end of cycle 6; ITT – intention-to-treat.
[a]All participants who were randomly assigned.
[b]All participants who were administered at least 1 dose of study medication.
[c]All participants from the BAT arm who crossed over to the fedratinib arm.
Source: BMS data on file.

3.2.6 Patient disposition in FREEDOM-2 and SACT

Patient disposition is shown in

Table 8. In the FREEDOM-2 fedratinib arm (N=134), at data cut-off, 43 (32%) were continuing on fedratinib and 91 (68%) had discontinued fedratinib. In the BAT arm (N=67), 3 (4%) were continuing on BAT, 18 (27%) had discontinued BAT without crossover, and 46 (69%) had crossed over to fedratinib. After crossover (N=46), 25 (54%) were continuing fedratinib and 21 (46%) had discontinued fedratinib. In SACT (N=54), at data cut-off, 27 (50%) were continuing on fedratinib and 27 (50%) had discontinued fedratinib. Deaths had occurred as follows: 43 (32%) in the fedratinib arm and 18 (27%) in the BAT arm of FREEDOM-2 had died, while 19 (35%) in SACT had died. Reasons for discontinuation are shown in Table 8. It is noted that whilst patients in FREEDOM-2 had to discontinue treatment on disease progression, this was a relatively uncommon reason for discontinuation of fedratinib (4% of fedratinib arm), with the most common reasons being adverse events (16% of fedratinib arm) and patient decision (13% of fedratinib arm). A CONSORT diagram for FREEDOM-2 is shown in CS Appendix D Figure 2.[2]

Table 8: Patient disposition (adapted from CS Appendix D Table 22 and CS Tables 22 and 24)

n (%)	FREEDOM-2				SACT
	Fedratinib (N=134)	BAT arm (N=67)			Fedratinib (N=54)
		BAT (incl. crossover to fedratinib) (N=67)	BAT (excl. crossover) (N=21)	Fedratinib (after crossover) (N=46)	
Enrolled and treated	134	67	21	46	54
Treatment ongoing	43 (32)	28 (42)	3 (4)	25 (54)	27 (50)
Discontinued study treatment	91 (68)	39 (58)	18 (27)	21 (46)	27 (50)
Died	43 (32)	18 (27%)	-	-	19 (35)
Died on treatment	-	-	-	-	7 (13)
Died not on treatment	-	-	-	-	12 (22)
Reason for discontinuation (% are for total N in arm):					
Death	13 (10)	6 (9)	1 (1)	5 (11)	12 (22)
Adverse event	22 (16)	8 (12)	4 (6)	4 (9)	7 (13)
Disease progression	6 (4)	4 (6)	2 (3)	2 (4)	6 (11)
Lack of efficacy	12 (9)	2 (3)	0 (0)	2 (4)	-
Patient decision	17 (13)	12 (18)	8 (12)	4 (9)	2 (4)
Physician decision	9 (7)	3 (4)	2 (3)	1 (2)	-
Other	12 (9)	4 (6)	1 (1)	3 (7)	-

Abbreviations: BAT - best available treatment.
Source: BMS data on file.

3.2.7 Baseline characteristics in fedratinib studies

Patient baseline characteristics in FREEDOM-2 and SACT are shown in Table 9. In FREEDOM-2, 76% of patients were intermediate-2 and 23% high risk, while in SACT 69% of patients were intermediate-2 and 31% high risk. Patient characteristics appeared similar between arms in FREEDOM-2, other than there being slightly more males in the fedratinib group (56%) than the BAT group (45%), and slightly more patients with at least 1 prior anti-cancer therapy (other than ruxolitinib) in the fedratinib group (20%) than the BAT group (10%).

Median baseline haemoglobin level was 9.3 to 9.4 g/dL, and baseline haemoglobin was ≤10g/dL in 67% (90/134) of the fedratinib arm and 61% (41/67) of the BAT arm (based on subgroup analysis presented in CS, Figure 35).[2] As noted in Chapter 2 of this EAG report, this suggests that at least 60% of the population of FREEDOM-2 could be classed as having moderate to severe anaemia at baseline, and may therefore overlap with the population eligible for momelotinib.

Overall, the baseline characteristics for FREEDOM-2 and SACT appear relevant to the NICE scope[1] and the company decision problem. The baseline characteristics in FREEDOM-2 appear broadly similar to those in SACT, suggesting that FREEDOM-2 is broadly generalisable to a UK population. There were some differences; there were more males in SACT (76%) than in FREEDOM-2 (52%), while median age was 70 years and 68 years in the two arms of FREEDOM-2 and 72 years in SACT.

Table 9: Baseline characteristics in FREEDOM-2 and SACT (adapted from CS Tables 6 and 12)

	FREEDOM-2		SACT
Characteristic	**Fedratinib (N = 134)**	**BAT (N = 67)**	**Fedratinib (N = 54)**
Median age, years (range)	70 (40-86)	68 (38-91)	72 (NR)
Age			
<40	-	-	2 (4%)
40 to 49	-	-	2 (4%)
50 to 59	-	-	4 (7%)
60 to 69	-	-	14 (26%)
70 to 79	-	-	26 (48%)
80+	-	-	6 (11%)
Sex, n (%)			
Male	75 (56%)	30 (45%)	41 (76%)
Female	59 (44%)	37 (55%)	13 (24%)
Race, n (%)			
White	106 (79%)	58 (87%)	-
Asian	9 (7%)	5 (8%)	-
American Indian or Alaska Native	0 (0%)	1 (2%)	-
Unknown	19 (14%)	3 (4%)	-
Median weight, kg (range)	72 (43-112)	66 (46-108)	-
Disease type, n (%)			
Primary myelofibrosis	75 (56%)	35 (52%)	30 (56%)
Post-polycythaemia vera	33 (25%)	21 (31%)	12 (22%)
Post-essential thrombocythaemia	26 (19%)	11 (16%)	12 (22%)
Risk status, n (%)[b]			
Intermediate-2	102 (76%)	51 (76%)	37 (69%)
High risk	30 (22%)	16 (24%)	17 (31%)
Missing	2 (2%)	0 (0%)	-
Median time since diagnosis, months (range)	43 (0-360)	58 (0-382)	-
At least 1 prior anti-cancer therapy other than ruxolitinib	27 (20%)	7 (10%)	-
JAK2/CALR/MPL variant status, n (%)			
Mutant	119 (89%)	64 (96%)	-
Triple negative	3 (2%)	0 (0%)	-
Incomplete testing	12 (9%)	3 (4%)	-
RBC transfusion dependence status, n (%)[a]			
Yes	29 (22%)	11 (16%)	-
No	105 (78%)	56 (84%)	-
Platelet count (10^9/L)			
n	129	64	-
Median (range)	124 (30-1,715)	117 (29-846)	-
Haemoglobin (g/dL)			
n	134	67	-
Median (range)	9.3 (5.7-14.4)	9.4 (6.5-14.0)	-
≤10 g/dL	90 (67%)	41 (61%)	-
>10 g/dL	44 (33%)	26 (39%)	-
ECOG PS, n (%)			
0	35 (26%)	20 (30%)	8 (15%) (29% of known)
1	76 (57%)	35 (52%)	15 (28%) (54% of known)
2	22 (16%)	11 (16%)	5 (9%) (18% of known)

	FREEDOM-2		SACT
Characteristic	**Fedratinib (N = 134)**	**BAT (N = 67)**	**Fedratinib (N = 54)**
3	1 (1%)	1 (2%)	0 (0%) (0% of known)
Missing			26 (48%)
Constitutional symptoms[b]			
Yes	84 (63%)	42 (63%)	-
No	50 (37%)	25 (37%)	-
Median baseline spleen volume, mL (range)[c]	2,622 (498-8,909)	2,693 (383-8,515)	-
Median baseline spleen size, cm (range)[d]	16 (5-37)	15 (4-40)	-

Abbreviations: BAT - best available therapy; CT - computed tomography; ECOG PS - Eastern Cooperative Oncology Group performance status; IPSS - International Prognostic Scoring System; IWG-MRT - International Working Group-Myeloproliferative Neoplasms Research and Treatment; ITT - intention to treat; JAK2 - Janus kinase 2; MPN-SAF - Myeloproliferative Neoplasm Symptom Assessment Form; MRI - magnetic resonance imaging; RBC - red blood cell.

[a]RBC transfusion dependence at baseline was defined per revised IWG-MRT criteria 2013.

[b]A participant had constitutional symptoms if any of the symptoms were in the baseline MPN-SAF (> 10% weight loss in 6 months, night sweat, unexplained fever > 37.5 °C).

[c]Baseline spleen volume by MRI/CT scan based on blinded central review.

[d]Baseline spleen size was measured by palpation (i.e., length in cm) below lower coastal region.

Source: BMS data on file.

3.2.8 Reasons for ruxolitinib discontinuation prior to FREEDOM-2 and SACT

Prior to enrolment in FREEDOM-2, 20% of patients were intolerant to ruxolitinib, 28% had a loss of response to ruxolitinib, and 27% never responded to ruxolitinib (other reasons are shown in Table 10). In SACT, 24% were intolerant to ruxolitinib and 76% had disease progression on ruxolitinib.

The EAG notes that in the BAT arm, 14/67 patients (21%) were intolerant to prior ruxolitinib (Table 10) while 52/67 (78%) were receiving ruxolitinib as part of BAT (Table 6), suggesting that virtually all patients who were not ruxolitinib-intolerant were likely to be receiving suboptimal ruxolitinib as part of BAT.

Table 10: Reasons for ruxolitinib discontinuation prior to FREEDOM-2 and SACT (adapted from CS Table 7)

Reason, n (%)	**FREEDOM-2**			**SACT**
	Fedratinib (N=134)	**BAT (N=67)**	**Total (N=201)**	**Fedratinib (N=54)**
Ruxolitinib AEs/intolerant	27 (20%)	14 (21%)	41 (20%)	13 (24%)
Disease progression on ruxolitinib	-	-	-	41 (76%)
Loss of response	38 (28%)	18 (27%)	56 (28%)	-
Never responded	40 (30%)	14 (21%)	54 (27%)	-
Partial response	3 (2%)	5 (7%)	8 (4%)	-
Other (physician decision, protocol requirement, trial end, course complete, missing)	26 (19%)	16 (24%)	42 (21%)	-

Abbreviations: AE - adverse event; BAT - best available therapy; ITT - intention to treat.

Note: Intolerance: haematological toxicity (anaemia, thrombocytopenia, other), non-haematological toxicity.

Source: BMS data on file.

3.2.9 Critical appraisal of fedratinib studies

The CS (Section B.2.5.1) outlines processes undertaken to minimise bias in the FREEDOM-2 RCT, but does not assess risk of bias using a validated checklist.[2] The company's clarification response (question A15) confirms that a critical appraisal has not been conducted by the company.[17] The EAG undertook a critical appraisal of FREEDOM-2 based on information in the study protocol. Criteria from the NICE Single Technology Appraisal user guide were used; these are similar to the criteria in the Cochrane Risk of Bias 2 tool for RCTs. The SACT dataset has not undergone formal quality assessment.

Risk of bias in FREEDOM-2 is summarised in Table 11. The study was adequately randomised and treatment allocation was adequately concealed. Groups were mostly similar at baseline, other than there being more males in the fedratinib group (56%) than BAT group (45%), and more with at least 1 prior anti-cancer therapy (other than ruxolitinib) in the fedratinib group (20%) than BAT group (10%). The latter may indicate that the fedratinib group were sicker than the BAT group. Participants and care providers were not blinded to treatment allocation. In terms of outcome assessment, there was blinded central review of MRI/CT scans for assessing spleen volume. All outcomes listed in the CSR were reported either in the CS or in the company's clarification response. All randomised patients were included in the primary analysis of spleen volume response. Overall, the EAG considers FREEDOM-2 to be at low risk of bias, other than the fact that participants and care providers were not blinded, which could have affected patient-reported outcomes such as symptom response and HRQoL.

Table 11: Critical appraisal of the FREEDOM-2 RCT

Criteria	Met?	Rationale and additional notes
Was randomisation carried out appropriately?	Yes	Used interactive response technology (IRT) and central laboratories
Was the concealment of treatment allocation adequate?	Yes	Used IRT and central laboratories
Were the groups similar at the outset of the study in terms of prognostic factors?	Mostly	Patient characteristics appeared similar between groups, other than there being slightly more males in the fedratinib group (56%) than BAT group (45%), and slightly more with at least 1 prior anti-cancer therapy (other than ruxolitinib) in the fedratinib group (20%) than BAT group (10%)
Were participants and care providers blind to treatment allocation?	No	Study was open-label
Were outcome assessors blind to treatment allocation?	Partly	Blinding of central review of MRI/CT scans for assessing spleen volume; however, local assessment of MRI/CT scans was not reported as being blinded
Were groups balanced in terms of dropouts?	Yes	All randomised patients were included in the primary analysis of spleen volume response.
Did the authors report all assessed outcomes?	Yes	All outcomes listed in the CSR were reported.
Did the analysis include an intention-to-treat analysis?	Yes	All randomised patients were included in the primary analysis of spleen volume response.

Abbreviations: BAT - best available therapy; IRT – interactive response technology; CSR – clinical study report; CT - computed tomography; MRI - magnetic resonance imaging.

3.3 Effectiveness of fedratinib

3.3.1 Spleen and symptom response at 6 months: FREEDOM-2

Response rates (for spleen volume or symptoms) at EOC6 (approximately 6 months) in FREEDOM-2 are shown in

Table 12. The primary outcome of spleen volume response rate (SVR ≥ 35% at EOC6) was 36% for fedratinib vs. 6% for BAT (p<0.0001). Symptom response rate (TSS reduction ≥ 50% at EOC6) was 34% for fedratinib vs. 17% for BAT (p=0.0033). A combined endpoint of spleen or symptom response was used in the company's economic model, with rates of 52% for fedratinib vs. 19% for BAT. Additional response outcomes are reported in CS Section B.2.6.1.[2]

Table 12: FREEDOM-2: Spleen volume response and symptom response at EOC6 (adapted from CS Table 13)

Outcome	Measure	Fedratinib (N=134)	BAT (N=67)	Difference, *p*-value[b]
Spleen volume response rate ≥ 35%	≥ 35% SVR at EOC6[a]	48 (36%)	4 (6%)	30%, *p*<0.0001
Spleen volume response rate≥ 25%	≥ 25% SVR at EOC6[a]	63 (47%)	9 (13%)	34%, *p*<0.0001
Symptom response rate	≥ 50% TSS reduction at EOC6[a]	43 (34%) [analysed N=126]	11 (17%) [analysed N=65]	17%, *p*=0.0033
Spleen volume **or** symptom response	≥ 35% SVR **or** ≥ 50% TSS reduction at EOC6[a]	70 (52%)	13 (19%)	33%, *p*=NR

Abbreviations: BAT - best available therapy; EOC6 - end of cycle 6; SVR - spleen volume reduction; TSS - total symptom score.
[a]Participants with missing assessment at EOC6, including those who met the criteria for progression of splenomegaly before EOC6, were considered non-responders. They were included in the denominator.
[b]Between-group difference according to stratified analysis based on electronic case report form.
Source: BMS data on file.

The company's rationale for using a combined endpoint of spleen or symptom response is that these outcomes track together (CS Section B.3.3.4).[2] Changes in spleen volume and TSS showed a Spearman's rank correlation of 0.304 (company's clarification response, question B9).[17] However, the EAG notes that, when categorising patients as responders using the specified cut-offs for the two measures, there was minimal agreement (Table 13). Spleen **or** symptom response occurred in 70 (52%) patients for fedratinib and 13 (19%) patients for BAT, whilst only 21 (16%) patients on fedratinib and 2 (3%) patients on BAT had both a spleen **and** symptom response (Table 13).

Table 13: Cross-tabulation for spleen and/or symptom responses

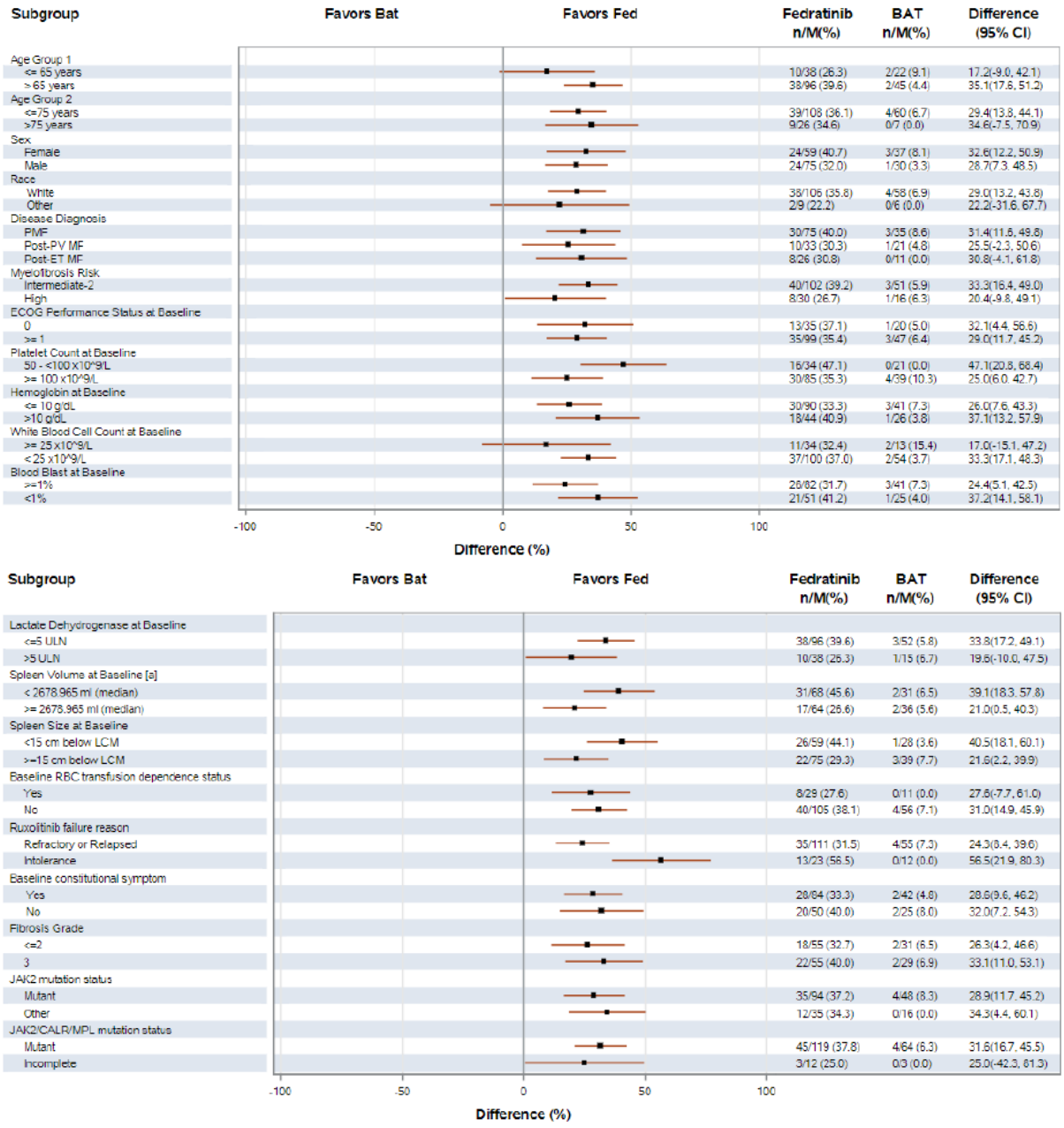
Fedratinib arm (N=134)			
	Symptom response	Symptom non-response	Total spleen response
Spleen response (SVR ≥ 35%)	Both: 21 (16%)	27	48
Spleen non-response	22	64	
Total symptom response	43		Either spleen or symptom response: 70 (52%)
BAT arm (N=67)			
	Symptom response	Symptom non-response	
Spleen response (SVR ≥ 35%)	Both: 2 (3%)	2	4
Spleen non-response	9	54	
Total symptom response	11		Either spleen or symptom response: 13 (19%)

Abbreviations: BAT - best available therapy; SVR - spleen volume reduction.

3.3.2 Subgroup analyses for spleen volume response at EOC6

Subgroup analyses were carried out on the primary outcome (spleen response rate, ≥ 35% SVR at EOC6). The CS states that the treatment effect was consistent across subgroups (Figure 2), but that a possibly larger treatment effect was observed in the subgroup with lower baseline platelet counts (50 to < 100 × 10^9/L) and the subgroup with ruxolitinib intolerance at baseline (as opposed to those relapsed or refractory to ruxolitinib).[2]

Figure 2: FREEDOM-2: Subgroup analysis for ≥ 35% SVR at EOC6, forest plot (reproduced from CS, Figure 35)



Abbreviations: BAT - best available therapy; CI - confidence interval; ECOG - Eastern Cooperative Oncology Group; EOC6 - end of cycle 6; ITT - intention to treat; JAK2 - Janus kinase 2; LCM - left costal margin; PMF - primary myelofibrosis; post-ET MF - post-essential thrombocythemia myelofibrosis; post-PV MF - post-polycythemia vera myelofibrosis; RBC - red blood cell; SVR - spleen volume reduction; ULN - upper limit of normal.
Source: BMS data on file [19].

3.3.3 Anaemia response and transfusion dependency

Table 14 summarises anaemia response and data on RBC transfusions and platelet transfusions (clarification response, question A21).[17] Anaemia response was defined as a ≥ 2 g/dL increase in haemoglobin level (in transfusion-independent patients at baseline) or transfusion independence (in transfusion-dependent participants at baseline). An anaemia response occurred in 20% of patients in the fedratinib arm and 23% of patients in the BAT arm (

Table 14).

Of patients who were RBC transfusion-dependent at baseline, transfusion independence during the study was achieved by 3% in the fedratinib arm and 18% in the BAT arm. Of patients who were transfusion-independent at baseline, the proportion becoming transfusion dependent during the study was 24% in the fedratinib arm and 34% in the BAT arm.

The table also reports the transfusion rate (units per patient per 28 days) for both RBC transfusion and platelet transfusion. However, the EAG notes that it is unclear whether transfusion rates are averaged across all randomised patients or only those who received a transfusion.

Table 14: FREEDOM-2: Anaemia response and red blood cell transfusion dependency (adapted from CS Section B.2.6.1.5 and clarification response Tables 4 and 5)

Outcome	Fedratinib (N=134)	BAT (N=67)
Anaemia response at any time[a]	20/101 (20%)	12/53 (23%)
RBC transfusion rate (unit per patient per 28 days): Mean (SD), N analysed[b]	1.935 (2.0898), N=96	1.408 (1.2085), N=42
Baseline RBC transfusion dependence[c] Dependent Independent	 29/134 (22%) 105/134 (78%)	 11/67 (16%) 56/67 (84%)
Postbaseline RBC transfusion independence [among patients **transfusion-dependent at baseline**][d,e] Dependent Independent	 28/29 (97%) 1/29 (3%)	 9/11 (82%) 2/11 (18%)
Postbaseline RBC transfusion dependence [among patients **NOT transfusion-dependent at baseline**][d,e, f] Dependent Independent	 25/105 (24%) 80/105 (76%)	 19/56 (34%) 37/56 (66%)
Platelets transfusion rate (unit per patient per 28 days): Mean (SD), N analysed[b]	0.487 (0.7253), N=20	2.843 (5.7614), N=7

Abbreviations: BAT - best available therapy; EOC6 - end of cycle 6; RBC - red blood cell; SVR - spleen volume reduction; SD- standard deviation; TSS - total symptom score.

[a]Anaemia response definition: A ≥ 2 g/dL increase in haemoglobin level (in transfusion-independent patients at baseline) or transfusion independence (in transfusion-dependent patients at baseline).

*[b]RBC transfusion rate = units of transfusions that occurred from first dose of study medication to last dose of study medication + 30 days/on-treatment period (days) * 28 days. For fedratinib arm, only participants initially randomly assigned to this arm are included. For BAT participants who crossed over, only data before crossover are included.*

[c]Transfusion dependence at baseline is defined as receiving ≥ 6 units of packed red blood cells, in the 12 weeks prior to study randomisation, for a haemoglobin level of < 85 g/L, in the absence of bleeding or treatment-induced anaemia. In addition, the most recent transfusion episode must have occurred in the 28 days prior to randomisation.

[d]Transfusion independence postbaseline is defined as absence of on-treatment RBC transfusion during any consecutive 'rolling' 12-week interval during the treatment phase, capped by a haemoglobin level of ≥ 85 g/L.

[e]Transfusion dependence at postbaseline is defined as receiving ≥ 6 units of packed red blood cells, in any consecutive 'rolling' 12-weeks interval during the treatment phase.

[f]The EAG notes that the CSR (Table 14.1.8.4.3) describes this outcome as "transfusion dependence" in those not dependent at baseline,[19] whereas the clarification response (A21) describes it as "transfusion independence" in those not dependent at baseline;[17] the EAG has assumed that the CSR is correct.

3.3.4 Time-to-event outcomes

Time-to-event outcomes are summarised in

Table 15 and discussed in the subsequent sections.

Table 15: Time-to-event outcomes

Outcome	FREEDOM-2				SACT	
	Fedratinib (N=134)		BAT (N=67)		Fedratinib (N=54)	
	N[c]	Median	N[c]	Median	N[c]	Median
Durability of spleen volume response (time from first ≥ 35% SVR to subsequent progressive disease in spleen volume as per IWG-MRT 2013 criteria, or death)[a]	72	86 weeks (19.8 months)	8	Not estimable	-	-
Durability of symptom response (time from first ≥ 50% TSS reduction to first documented TSS reduction <50%)[b]	90	12 weeks (2.8 months)	32	10 weeks (2.3 months)	-	-
Time to treatment discontinuation (TTD)	134	[redacted] weeks ([redacted] months)	67	[redacted] weeks ([redacted] months)	54	25 weeks (5.7 months)
Spleen and disease progression-free survival (SDPFS)	134	112 weeks (25.8 months)	67	Not estimable	-	-
Overall survival (OS)	134	Not estimable	67	125 weeks (28.8 months)	54	67 weeks (15.4 months)

Abbreviations: BAT - best available therapy; SVR - spleen volume reduction; OS- overall survival; SDPFS - Spleen and disease progression-free survival; TSS - total symptom score.
[a]CSR Section 3.6.3.6;[19] [b]CSR Section 3.6.3.8;[19] [c]N analysed

3.3.5 Durability of spleen and symptom response

Durability of spleen and symptom response in FREEDOM-2 are shown in

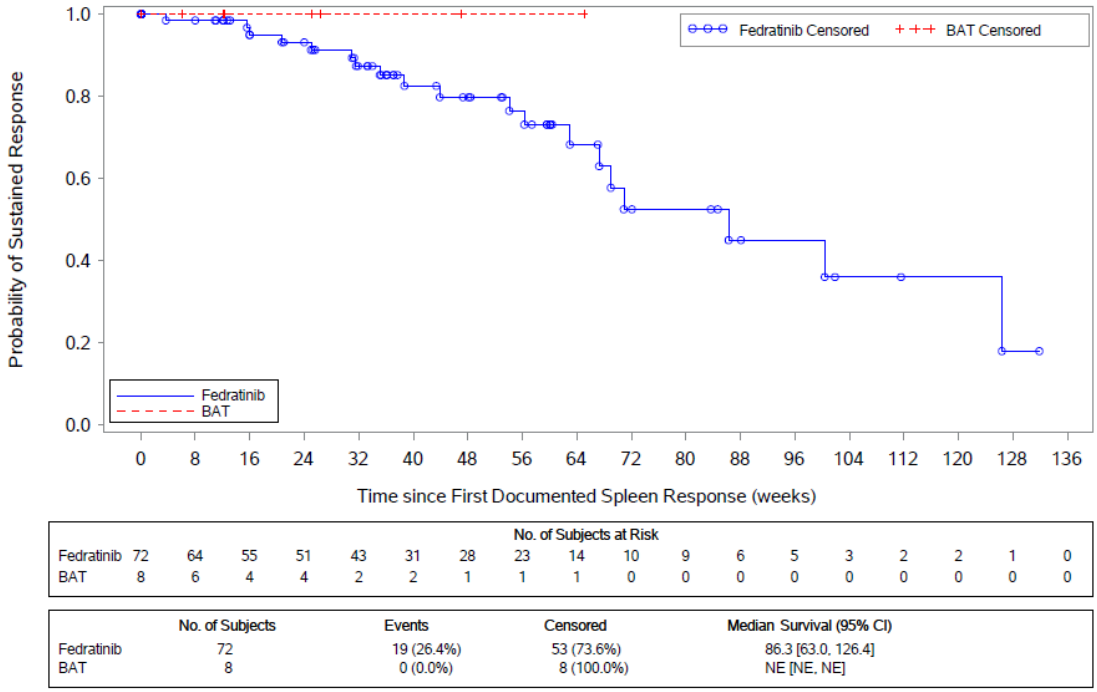
Table 15, Figure 3 and Figure 4. For spleen volume response (Figure 3), in the fedratinib arm, 72 patients (54%) had a spleen volume response at any time, and median durability of response was 86 weeks; while in the BAT arm, 8 (12%) had a spleen volume response at any time, and median durability of response was not estimable because no patient had an event (see below). For symptom response (Figure 4), in the fedratinib arm, 90 (67%) of patients had a symptom response at any time, and median durability of response was 12 weeks; while in the BAT arm, 32 (48%) had a symptom response at any time, and median durability of response was 10 weeks.

The EAG notes a number of points on these analyses. Firstly, they include patients having a response at any time and are not restricted to responders at EOC6, therefore the numbers of patients analysed for response duration (

Table 15) are greater than the numbers with a response at EOC6 (

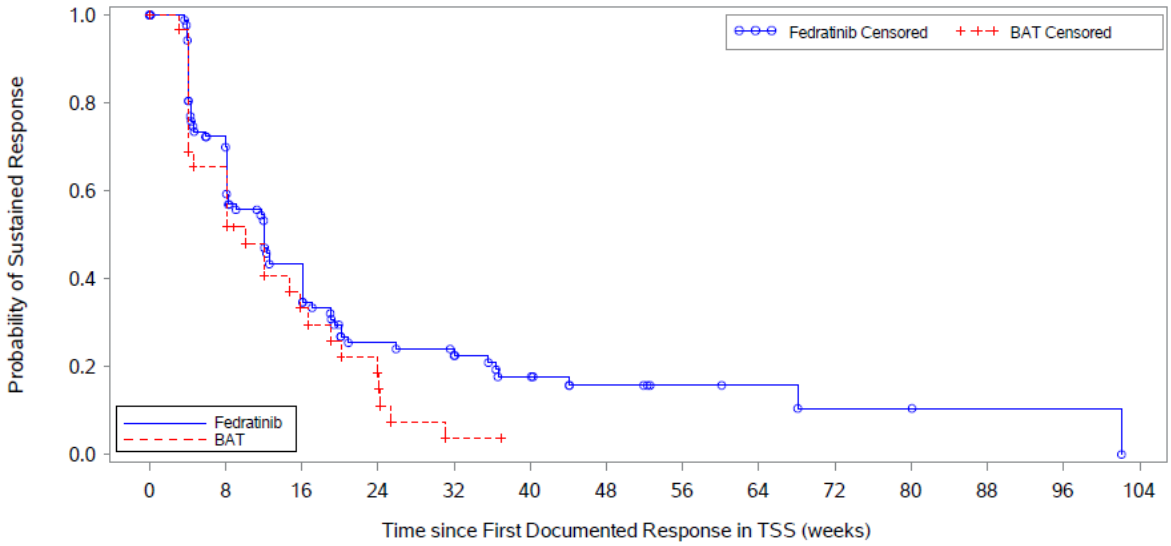
Table 12). Secondly, durability of symptom response ends when there is a documented TSS reduction less than 50%; conversely, durability of spleen response does not end when the spleen volume reduction becomes less than 35%, but instead continues until either death or documented progressive disease in spleen volume as per IWG-MRT 2013 criteria (defined elsewhere as a ≥ 25% increase in spleen volume). Thirdly, the CSR (Section 3.6.3.6)[19] states that response duration was censored at crossover or new anti-myelofibrosis therapy, whereas the clarification response (A19) states that these outcomes were not censored for crossover,[17] so censoring remains unclear. Fourthly, the EAG queried whether symptom response may fluctuate over time which may impact its usefulness in assessing durability of response, but the company declined to respond to this question (clarification response question A20).[17]

Figure 3: FREEDOM-2: Kaplan-Meier plot of durability of spleen volume response by MRI/CT scan (reproduced from CS, Figure 6)



Abbreviations: BAT - best available therapy; CI - confidence interval; CT - computed tomography; ITT - intention to treat; MRI - magnetic resonance imaging; NE - not estimable.
Source: BMS data on file.

Figure 4: FREEDOM-2: Kaplan-Meier plot of durability of symptom response (reproduced from CS, Figure 8)



No. of Subjects at Risk

Fedratinib	90	61	35	18	16	11	7	4	3	2	2	1	1	0
BAT	32	19	9	6	1	0	0	0	0	0	0	0	0	0

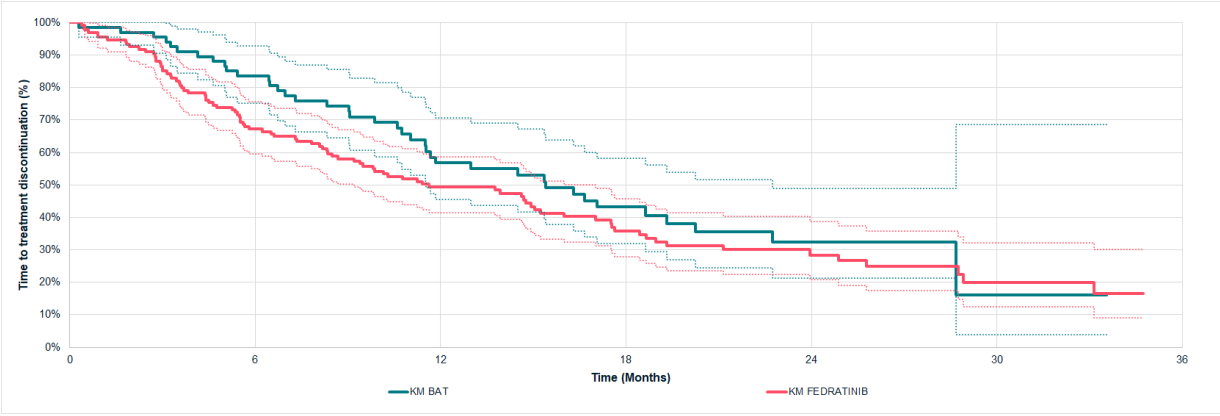
	No. of Subjects	Events	Censored	Median Survival (95% CI)
Fedratinib	90	70 (77.8%)	20 (22.2%)	12.1 [8.1, 16.1]
BAT	32	27 (84.4%)	5 (15.6%)	10.1 [4.1, 16.7]

Abbreviations: BAT - best available therapy; CI - confidence interval; ITT - intention to treat; TSS - total symptom score.
Source: BMS data on file.

3.3.6 Time to treatment discontinuation (TTD)

Time to treatment discontinuation (TTD) in FREEDOM-2 is shown in Figure 5 (note that unlike other figures, the fedratinib arm is in red and BAT arm in blue). The median TTD was [redacted] weeks ([redacted] months) for fedratinib and [redacted] weeks ([redacted] months) for BAT (clarification response, question B18).[17] In the BAT arm, 69% of patients crossed over to fedratinib at 6 months, and the CS (Section B.3.3.6) suggests that there was no censoring for crossover,[2] as the company presents analyses excluding patients with treatment switching as an alternative approach. The company's response to clarification (question B18b) confirmed that crossover was not considered an event in terms of treatment discontinuation.[17]

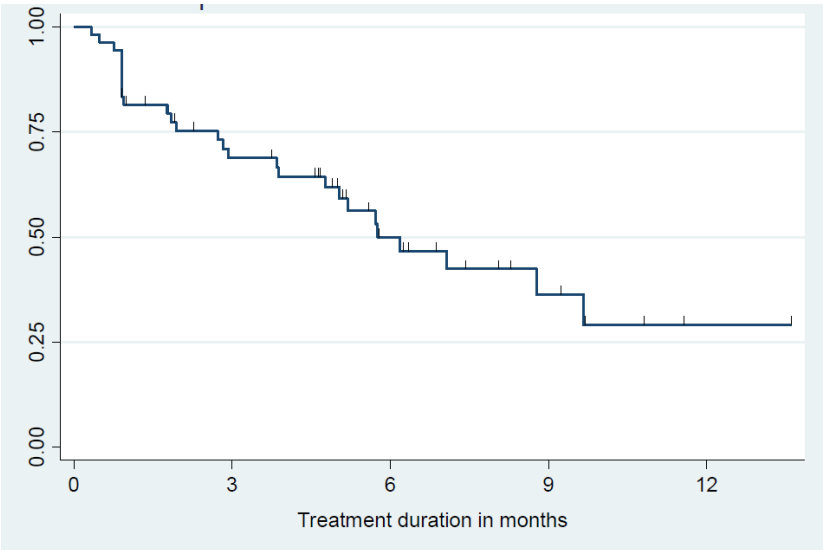
Figure 5: Time to treatment discontinuation in FREEDOM-2 (reproduced from CS, Figure 38)



Abbreviations: BAT - best available therapy; KM - Kaplan-Meier; TTD - time to treatment discontinuation.

TTD in SACT is shown in Figure 6; the median TTD was 25 weeks (5.7 months). The company confirmed that the outcome of treatment duration in SACT was equivalent to TTD in FREEDOM-2 (clarification response, question A25).[17] The EAG queried why TTD in SACT might be [redacted] TTD in the FREEDOM-2 fedratinib arm. The company responded (clarification response, question A25) that this may be due to SACT being a real-world dataset with diverse characteristics, comorbidities, and treatment histories, as well as a smaller cohort.[17]

Figure 6: Time to treatment discontinuation in SACT (reproduced from CS, Figure 33)



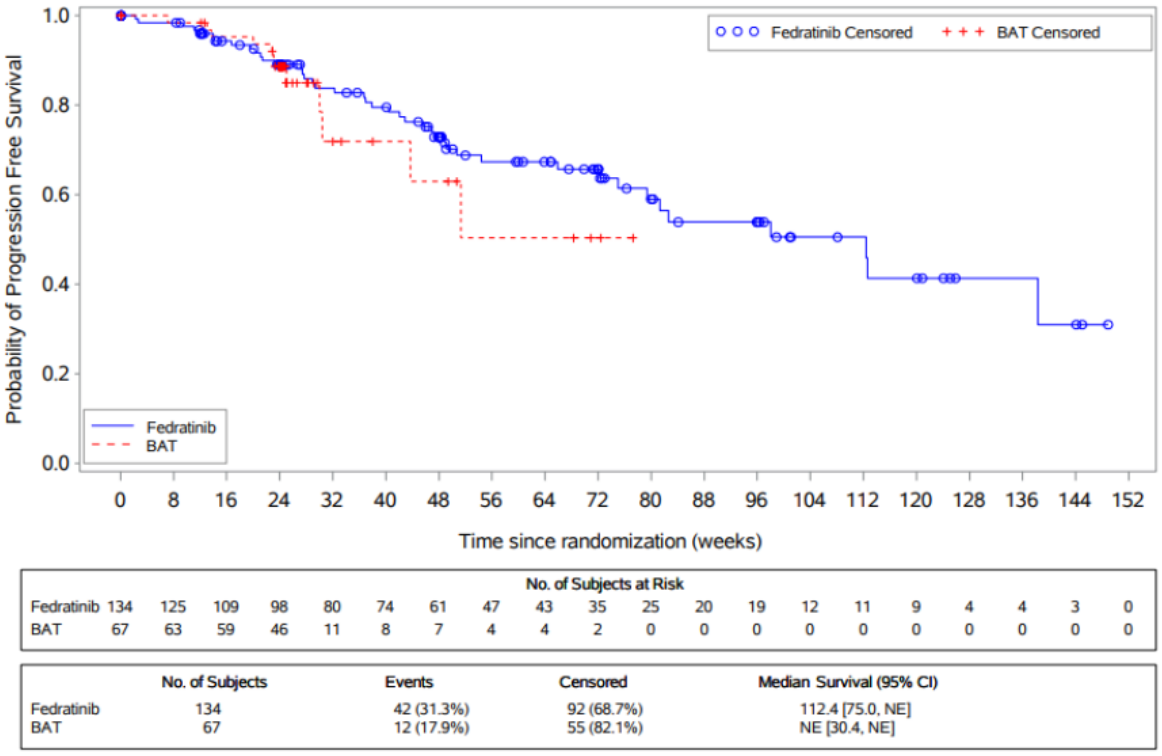
Abbreviations: SACT - Systemic Anti-Cancer Therapy.
Source: NHS England data on file.

3.3.7 Spleen and disease progression-free survival (SDPFS)

Spleen and disease progression-free survival (SDPFS) for FREEDOM-2 is shown in Figure 7. The median SDPFS was 112 weeks (25.8 months) for fedratinib and not estimable for BAT. Relevant events were reported for 42 (31%) patients in the fedratinib group and 12 (18%) in the BAT group. The

company's clarification response (question A19) states that there was no censoring for crossover;[17] however, the CSR (Section 3.6.3.9)[19] states that patients were censored at the point of initiation of new anti-myelofibrosis therapy; therefore this remains unclear.

Figure 7: FREEDOM-2: Spleen and disease progression-free survival (SDPFS, reproduced from CS, Figure 9)

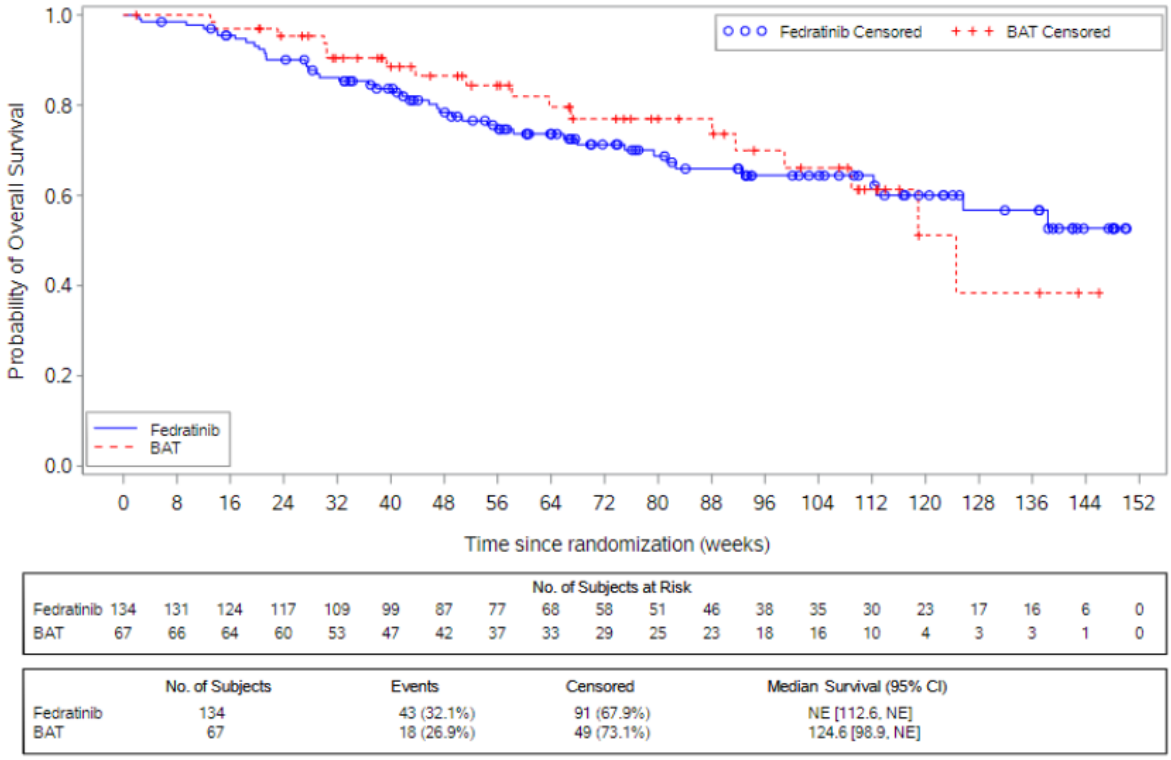


Abbreviations: BAT - best available therapy; CI - confidence interval; ITT - intention to treat; NE - not estimable.
Source: BMS data on file.

3.3.8 Overall survival

OS for FREEDOM-2 is shown in Figure 8. The CS notes that 69% of patients in the BAT group crossed over to fedratinib by 6 months, and the analysis is not censored or adjusted for crossover.[2] The median OS was not estimable (95% CI: 113 weeks to not estimable) for fedratinib and 125 weeks (28.8 months; 95% CI: 99 weeks to not estimable) for BAT. Deaths were reported for 43 (32%) patients in the fedratinib group and 18 (27%) patients in the BAT group.

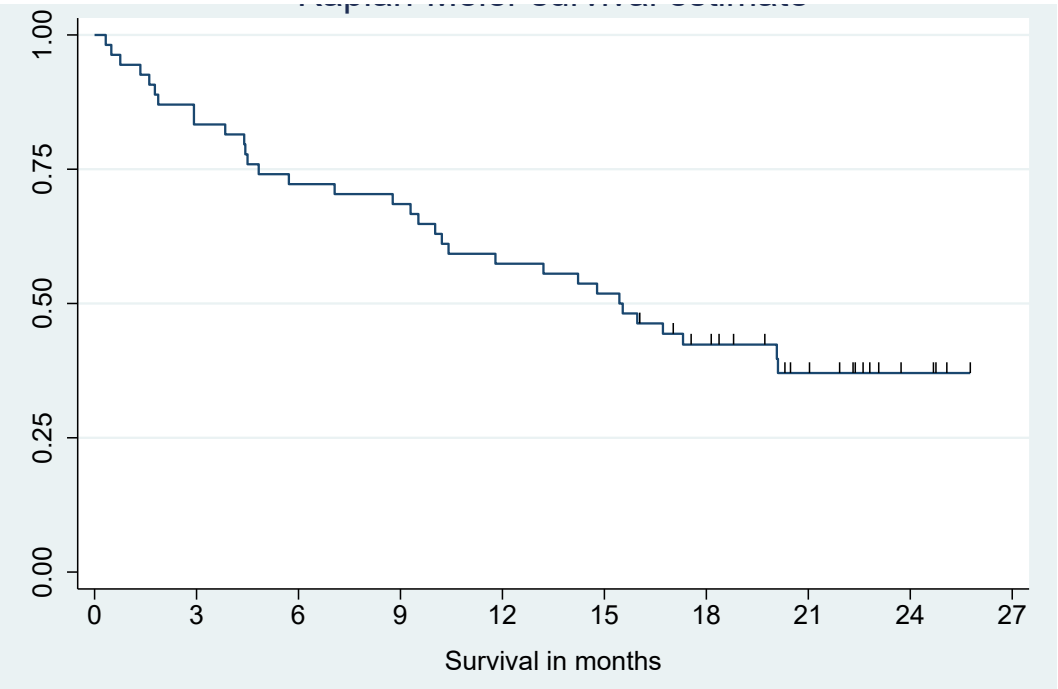
Figure 8: FREEDOM-2: overall survival (reproduced from CS, Figure 10)



Abbreviations: BAT - best available therapy; CI - confidence interval; ITT - intention to treat; NE - not estimable.
Source: BMS data on file.

OS in SACT is shown in Figure 9. Median OS was 67 weeks (15.4 months). The EAG queried why OS in SACT might be shorter than OS in the FREEDOM-2 fedratinib arm. The company responded (clarification response, question A26) that the SACT dataset includes older patients than FREEDOM-2 (though the EAG does not agree that this can be determined from the baseline data), that SACT has more male patients (76% in SACT, 56% in FREEDOM-2), and that the treatment duration is [redacted] in SACT than FREEDOM-2.[17] The company also noted that ECOG PS was missing for a substantial proportion of the SACT dataset (48%), making it difficult to compare disease burden, and that real-world studies carry higher uncertainty. However, the EAG considers that none of these factors adequately explain the difference in OS.

Figure 9: SACT: overall survival (reproduced from CS, Figure 34)



Abbreviations: SACT - Systemic Anti-Cancer Therapy.
Source: NHS England data on file.

3.3.9 Overall survival crossover adjustment: FREEDOM-2

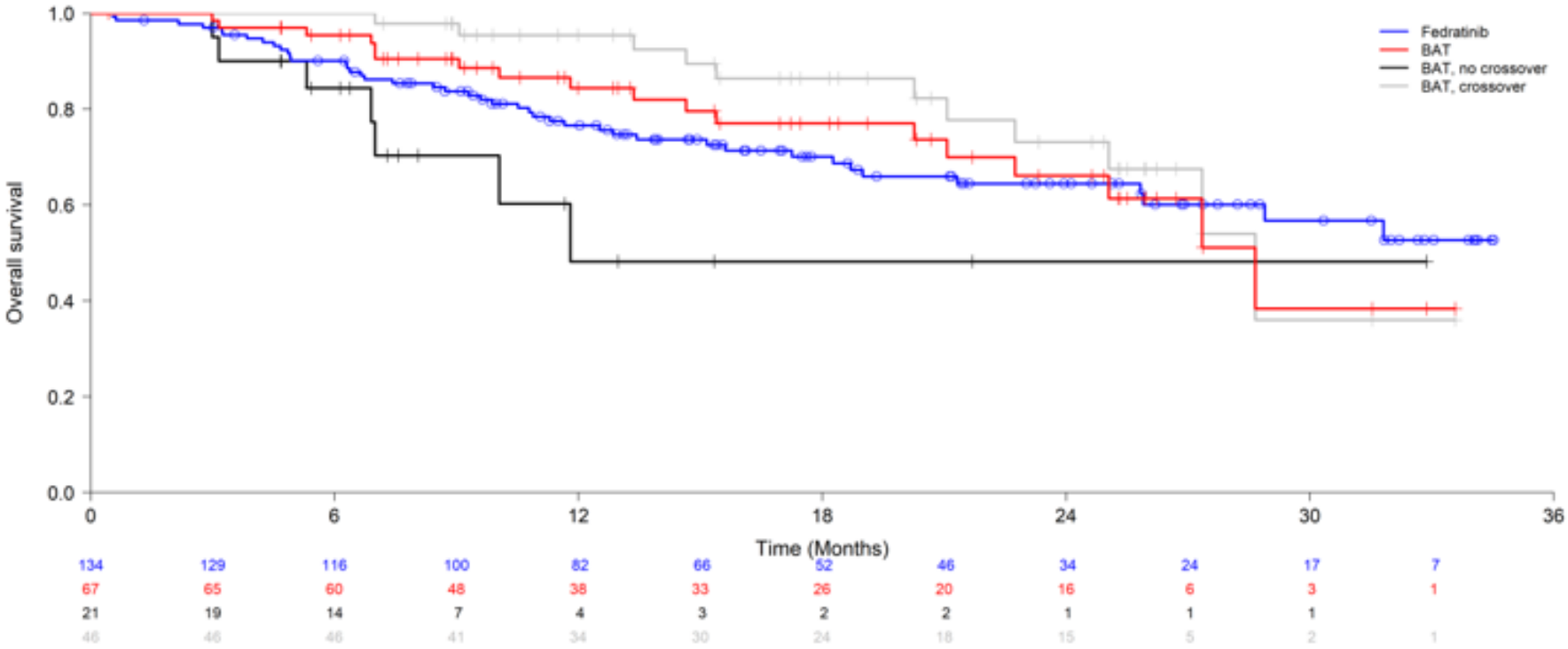
Summary of company's adjustment for treatment switching

The company undertook a set of exploratory analyses to adjust for crossover from BAT to fedratinib. Results of the company's analyses are described in CS Section B.2.6.1.6[2] with further detail provided in the company's technical report on crossover adjustment.[21]

Out of the 67 patients randomised to receive BAT, 46 (69%) crossed over to receive fedratinib. The majority of the patients who switched to fedratinib, 43 (93%) did so after 6 cycles and the remaining 3 switched earlier, after progression. Median time to switching was 6.3 months (range 5.5-17.5 months). Over the full course of the study, death was reported for 43 of the 134 patients (32.1%) in the fedratinib group and 18 of the 67 patients (26.9%) in the BAT group.

Figure 10 shows OS for the treatment groups as randomised, together with the BAT group stratified by switching status. OS is similar for both groups with the BAT group actually showing slightly higher OS estimates compared to fedratinib until the curves cross at approximately 24 months. When the Kaplan-Meier (KM) estimates for BAT are stratified according to crossover status, more favourable OS estimates are observed for those who cross over, compared to those who do not (although as only 21 patients did not cross over to receive fedratinib, the OS estimates are very uncertain).

Figure 10: Overall survival Kaplan-Meier for fedratinib and BAT ITT populations and BAT stratified by crossover status (reproduced from CS, Figure 28)



Abbreviations: BAT - best available therapy. Source: BMS data on file.

The company discussed five potential methods for adjusting for treatment switching: rank-preserving structure failure time (RPSFT) models with and without re-censoring, iterative parameter estimation (IPE), simplified 2-stage estimation (TSEsimp), complex 2-stage estimation with g-estimation (TSEgest), and inverse probability of censoring weighting (IPCW). Three of these methods (RPSFT, TSEsimp, IPCW) were applied to the data and are summarised in the CS. The remaining two methods (IPE and TSEgest) were not considered with the CS stating challenges with the methods in this application.[2]

The selection of prognostic factors to contribute to the analyses is described in the company's technical report on crossover adjustment.[21] The five factors prioritised for crossover adjustment analysis were: ECOG PS (time-varying), RBC transfusion dependence status (time-varying), myelofibrosis subtype (baseline), DIPSS risk (baseline), and response to prior ruxolitinib treatment (baseline).

The company's description of the three considered methods has been summarised by the EAG below. Briefly, the company concludes that none of the methods are appropriate due to likely violation of the assumptions of each method, small sample sizes, and contradictory results of the three methods.

- Rank-preserving structure failure time **(RPSFT)** resulted in a slightly improved OS for the control group (CS, Figure 29).[2] The company considered that this result lacked face validity.
- Simplified 2-stage estimation (**TSEsimp)** was applied using the 5 listed covariates above. The secondary baseline was defined as cycle 6 (after which the majority of patients switched).[21] Five different accelerated failure time models were applied with all models estimating acceleration factors that are close to zero (CS Table 21),[2] implying a much longer survival time for switchers, and resulting in adjusted OS estimates that essentially truncate the survival time in participants who crossed over to the point at which cross-over occurred. Adjusted KM OS curves are shown in CS, Figure 30,[2] but the company considers that these are biased due to estimated AFs lacking face validity.
- Inverse probability of censoring weighting **(IPCW)** was applied using all 5 listed covariates apart from myelofibrosis subtype as the model for calculating the weights failed to converge when all covariates were included. The distribution of weights was considered reasonable (median weight, 0.99; range, 0.46-2.19). However, the short-term follow-up of the 21 BAT patients who did not cross-over to receive fedratinib was stated as a major limitation. IPCW adjusted OS curves are presented in CS, Figure 31.[2] These are very similar to the naïve approach of censoring patients at the time of treatment-switching.

EAG critique of adjustment for treatment switching

When the KM estimates for BAT are stratified according to crossover status, more favourable OS estimates are observed for those who cross-over, compared with those who do not (although as only 21

patients did not cross over to receive fedratinib, the OS estimates are very uncertain). This suggests that crossover is likely to be based on prognostic characteristics, with patients who have a better prognosis being more likely to switch to fedratinib. Censoring at the time of switching is likely to favour fedratinib as this is essentially taking the participants with better prognosis out of the control group.

IPCW would normally be recommended in this case, to upweight the BAT participants who did not switch that have similar characteristics to those who did switch. However, IPCW requires good availability of prognostic covariates measured over time and the analyses conducted by the company have been limited by small sample size. Results were very similar to the naïve approach, demonstrating only a minimal impact of adjustment.

The EAG therefore considers that the company's conclusion is appropriate and that none of the results are recommended.

Since formal adjustment for treatment switching was not considered appropriate and the observed OS and TTD in FREEDOM-2 was similar across treatment groups (Figure 5 and Figure 8), the company's base-case model uses data pooled across the fedratinib and BAT treatment groups (see Section 4.2.5.1) thereby assuming equivalent OS in each treatment group. The EAG considers this assumption to be reasonable given the data.

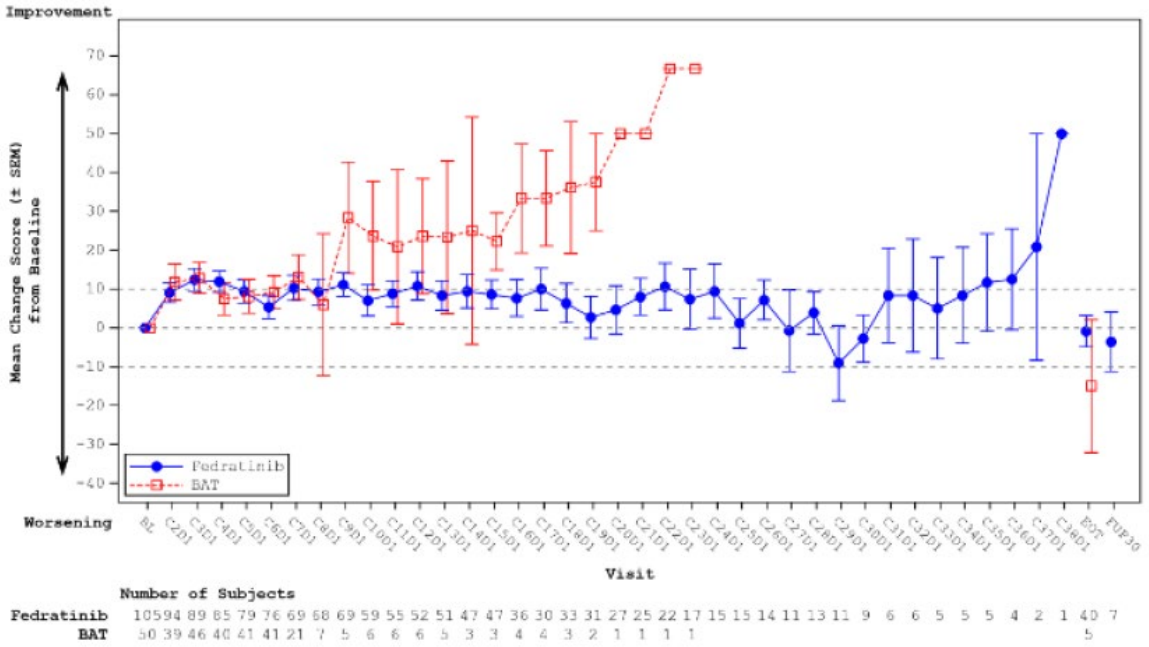
3.3.10 Health-related quality of life

The CS reports HRQoL via the EORTC QLQ-C30 and the EQ-5D-5L (CS Section B.2.6.1).[2] The EORTC QLQ-C30 measures various domains on a 0-100 scale where a 10-point change is considered clinically meaningful. Domains include a global health scale (100 is best), five functional scales (physical, role, emotional, cognitive and social; 100 is best) and nine individual symptom scales/items (100 is worst). The EQ-5D-5L has five items (assessing mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) which can be combined into a single utility index (where 1 is full health, 0 is equivalent to death and values below 0 are considered as state worse than death), as well as a VAS for global health (0-100 where 100 is best).

EORTC QLQ-C30 results: For EORTC QLQ-C30 global health status (Figure 11), there were similar increases from baseline in the fedratinib and BAT groups of just over 10 units (clinically meaningful change) within the first 2-3 months, but little difference between groups. Scores then fluctuated up to EOC6 with little clear difference between groups. After EOC6, there was a trend towards better scores for BAT than fedratinib, but this was based on very small numbers of patients in the BAT group. The five functional scales (physical, role, emotional, cognitive and social) showed similar results (CS Section B.2.6.1).[2] The company's clarification response (question A19) states that there was no

censoring for crossover.[17] However, the EAG notes that the number of analysed patients in the BAT group drops suddenly at EOC6; therefore, it is unclear whether BAT scores after EOC6 include patients who crossed over to fedratinib. This makes the data difficult to interpret.

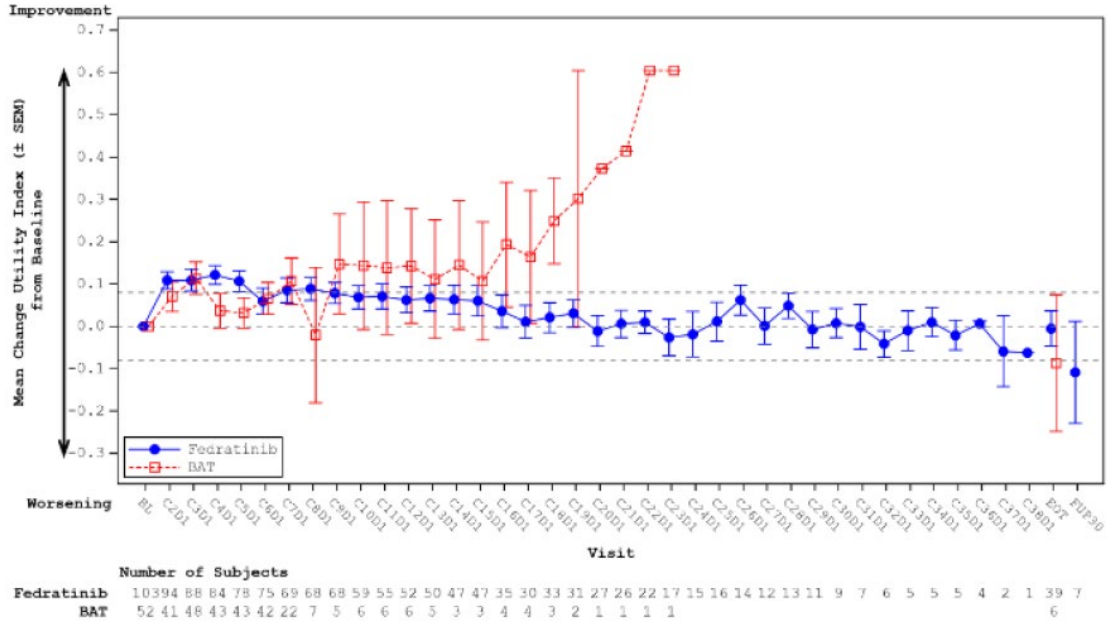
Figure 11: FREEDOM-2: EORTC QLQ-C30 Global Health Status, mean change from baseline (reproduced from CS, Figure 11)



EOC6 is represented as C7D1 on the x axis.
Abbreviations: BAT - best available therapy; BL - baseline; EORTC QLQ-C30 - European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Quality of Life of Cancer Patients (Core); EOT - end of treatment; HRQOL - health-related quality of life; MID - minimally important difference; QOL - quality of life; SEM - standard error of mean.
Note: Horizontal reference lines indicate MID, considered a change of ± 10 points from baseline.
Source: BMS data on file.

EQ-5D-5L results: For the EQ-5D-5L utility index (Figure 12), there were increases from baseline in both groups up to EOC6, with clinically meaningful improvements (greater than 0.07) at certain points in both groups. After EOC6, there was a trend towards better scores for BAT than fedratinib, but this was based on very small numbers of patients for BAT. The EQ-5D-5L VAS showed similar results (CS, Figure 26).[2] Again, the company's clarification response (question A19) states that there was no censoring for crossover.[17] However, the EAG notes that the number of analysed patients in the BAT group drops suddenly at EOC6; therefore, it is unclear whether BAT scores after EOC6 include patients who crossed over to fedratinib. Again, this makes the data difficult to interpret.

Figure 12: FREEDOM-2: EQ-5D-5L utility index, mean change from baseline (reproduced from CS, Figure 27)



EOC6 is represented as C7D1 on the x axis.
Abbreviations: BAT - best available therapy; BL - baseline; EOT - end of treatment; HRQOL - health-related quality of life; SEM - standard error of mean.
Source: BMS data on file.

3.3.11 Additional clinical outcomes

The CS also reports the following outcomes for FREEDOM-2 in Section B.2.6.1: spleen response by palpation; durability of spleen response by palpation; time to spleen response by palpation; and best spleen volume response.[2] These are not summarised here as the EAG considers that the outcome of response rate specified in the scope is adequately addressed by the data in Section 3.3.1, and these additional clinical outcomes do not inform the company's economic model.

3.4 Safety of fedratinib

3.4.1 Studies providing safety data on fedratinib

The CS reports safety data from FREEDOM-2 (CS Section B.2.10) but not from SACT.[2] The safety population for FREEDOM-2 included all randomised patients (N=201). Safety data are provided for three groups separately: the fedratinib "all-treated" group (N=134), the BAT "all-treated" group (N=67), and the fedratinib after crossover group (N=46). The company's clarification response (question A27) confirms that the BAT "all-treated" group only includes data before crossover.[17]

3.4.2 Treatment exposure

The mean duration of treatment exposure was 53 weeks in the fedratinib arm, 42 weeks in the fedratinib crossover group, and 28 weeks in the BAT arm (not including crossover). The median duration of treatment exposure was 43 weeks in the fedratinib arm, 39 weeks in the fedratinib crossover group, and

25 weeks in the BAT arm (not including crossover). Mean relative dose intensity (RDI) was 86.9% and 90.5% in the fedratinib arm and the fedratinib crossover group, respectively.

3.4.3 Overview of safety of fedratinib

A summary of safety data is provided in Table 16. In FREEDOM-2, treatment-emergent AEs (TEAEs) occurred in 99% and 100% with fedratinib (all-treated and crossover) and 97% with BAT (no crossover). Grade 3 or 4 AEs were reported in 77% and 67% with fedratinib (all-treated and crossover) and 55% with BAT. Serious AEs were reported in 54% and 35% with fedratinib (all-treated and crossover) and 31% with BAT. AEs leading to death were reported in 16% and 9% with fedratinib (all-treated and crossover) and 6% with BAT (there were no reported treatment-related AEs leading to death).

Table 16: FREEDOM-2: Safety overview (adapted from CS Table 27)

	Overview of AEs: N (%)		
	Fedratinib (N=134)	**Fedratinib crossover (N=46)**	**BAT (N=67)**
TEAEs	132 (99)	46 (100)	65 (97)
Treatment-related TEAEs	116 (87)	44 (96)	24 (36)
Grade 3 or 4 TEAEs	103 (77)	31 (67)	37 (55)
Treatment-related grade 3 or 4 TEAEs	62 (46)	18 (39)	10 (15)
TEAE leading to death	21 (16)	4 (9)	4 (6)
Treatment-related TEAE leading to death	NR	NR	NR
Treatment-emergent serious AEs	72 (54)	16 (35)	21 (31)
Treatment-related treatment-emergent serious AEs	25 (19)	5 (11)	2 (3)
TEAEs leading to permanent treatment discontinuation	24 (18)	7 (15)	4 (6)
TEAEs leading to dose modification	NR	NR	NR
TEAEs leading to dose reduction	48 (36)	18 (39)	7 (10)
TEAEs leading to dose interruption	52 (39)	15 (33)	4 (6)

Abbreviations: BAT - best available therapy; NR - not reported; TEAE - treatment-emergent adverse event.
Note: For the fedratinib group, only data for participants who were initially treated with fedratinib are summarised. For crossover participants in the BAT arm, only data before crossover are included.
Source: FREEDOM-2 CSR.[19]

3.4.4 Common AEs

Common AEs are reported in the CS (CS Tables 28 and 29).[2] Common AEs with occurrence ≥15% in any group, and treatment-related AEs with occurrence ≥5% in any group, are shown in Table 17. The most common AEs in the fedratinib arm were diarrhoea (46%), anaemia (44%), nausea (40%), thrombocytopenia (36%), constipation (22%) and asthenia (20%), with a similar pattern in the fedratinib crossover group. In the BAT group (no crossover), the most common AEs were anaemia (36%), asthenia (24%), thrombocytopenia (18%), nausea (15%), pruritus (15%) and fatigue (15%).

Table 17: FREEDOM-2: Common treatment-emergent AEs (≥15%) and treatment-related AEs (≥5%) (adapted from CS Tables 28 and 29)

	Treatment-emergent AEs: N (%)			Treatment-related AEs: N (%)		
	Fedratinib (N=134)	**Fedratinib crossover (N=46)**	**BAT (N=67)**	**Fedratinib (N=134)**	**Fedratinib crossover (N=46)**	**BAT (N=67)**
Participants with at least 1 TEAE	131 (98)	46 (100)	58 (87)	103 (77)	38 (83)	13 (19)
Anaemia	59 (44)	20 (44)	24 (36)	22 (16)	14 (30)	9 (13)
Thrombocytopenia	48 (36)	13 (28)	12 (18)	32 (24)	10 (22)	4 (6)
Diarrhoea	62 (46)	17 (37)	3 (4)	54 (40)	15 (33)	-
Nausea	54 (40)	11 (24)	10 (15)	45 (34)	11 (24)	1 (1)
Vomiting	25 (19)	9 (20)	3 (4)	19 (14)	7 (15)	1 (1)
Constipation	30 (22)	6 (13)	6 (9)	12 (9)	-	3 (4)
Asthenia	27 (20)	8 (17)	16 (24)	-	-	-
Oedema peripheral	26 (19)	6 (13)	7 (10)	-	-	-
COVID-19	21 (16)	12 (26)	7 (10)	-	-	-
Pruritus	20 (15)	5 (11)	10 (15)	-	-	-
Fatigue	11 (8)	4 (9)	10 (15)	-	-	-
ALT increased	11 (8)	-	1 (1)	10 (7)	-	-
Blood creatinine increased	17 (13)	4 (9)	1 (1)	10 (7)	-	-
Vitamin B1 decreased	17 (13)	4 (9)	2 (3)	11 (8)	-	-
Abdominal pain	16 (12)	7 (15)	9 (13)	-	-	-
Vitamin B1 deficiency	10 (7)	-	1 (1)	7 (5)	-	-
Night sweats	8 (6|)	7 (15)	9 (13)	-	-	-
Renal failure	7 (5)	3 (7)	-	-	3 (7)	-
Pneumonia	6 (4)	4 (9)	5 (7)	-	3 (7)	-

Abbreviations: AE - adverse event; ALT - alanine aminotransferase; AST - aspartate aminotransferase; BAT - best available therapy; TEAE - treatment-emergent adverse event.
For the fedratinib arm, only participants who initially were randomly assigned to fedratinib are included. For crossover participants in BAT arm, only data before crossover are included.
Source: BMS data on file.

3.4.5 Grade 3 and 4 AEs and serious AEs

Grade 3 and 4 AEs are reported in the company's clarification response (question A27, Tables 6 and 7).[17] Grade 3 and 4 AEs and treatment-related AEs with occurrence ≥3% in any group are shown in Table 18. The most common grade 3 and 4 AEs in the fedratinib arm were anaemia (32%), thrombocytopenia (27%), hyperkalaemia (8%), general physical health deterioration (8%) and acute kidney injury (7%). In the BAT group (no crossover), the most common grade 3 and 4 AEs were anaemia (21%), thrombocytopenia (7%) and leukocytosis (6%). Serious AEs are reported in CS Tables 30 and 31, and AEs leading to death in CS Table 35.[2]

Table 18: FREEDOM-2: Grade 3/4 AEs and treatment-related AEs (≥3%) (adapted from company's clarification response, Tables 6 and 7)

	Grade 3/4 AEs: N (%)			Treatment-related Grade 3/4 AEs: N (%)		
	Fedratinib (N=134)	**Fedratinib crossover (N=46)**	**BAT (N=67)**	**Fedratinib (N=134)**	**Fedratinib crossover (N=46)**	**BAT (N=67)**
Participants with ≥ 1 CTCAE Grade 3/4 TEAE	103 (77)	31 (67)	37 (55)	62 (46)	18 (39)	10 (15)
Anaemia	43 (32)	13 (28)	14 (21)	13 (10)	8 (17)	6 (9)
Thrombocytopenia	36 (27)	12 (26)	5 (7)	23 (17)	9 (20)	3 (4)
Leukocytosis	4 (3)	1 (2)	4 (6)	-	-	-
Neutropenia	4 (3)	3 (7)	1 (1)	3 (2)	-	1 (1)
Hyperkalaemia	11 (8)	1 (2)	-	4 (3)	-	-
Decreased appetite	4 (3)	-	1 (1)	2 (1)	-	-
Pneumonia	3 (2)	2 (4)	3 (4)	-	1 (2)	1 (1)
COVID-19	2 (1)	3 (7)	3 (4)	-	-	-
Urinary tract infection	2 (1)	3 (7)	-	-	-	-
Acute kidney injury	9 (7)	-	1 (1)	3 (2)	-	-
Chronic kidney disease	5 (4)	2 (4)	-	5 (4)	1 (2)	-
Renal failure	4 (3)	1 (2)	-	3 (2)	1 (2)	-
General physical health deterioration	11 (8)	1 (2)	1 (1)	2 (1)	-	-
Asthenia	4 (3)	3 (7)	1 (1)	2 (1)	1 (2)	-
Fatigue	2 (1)	-	2 (3)	-	-	-
Pyrexia	-	-	2 (3)	-	-	-
Alanine aminotransferase increased	6 (4)	-	-	5 (4)	-	-
Cardiac failure	4 (3)	-	1 (1)	-	-	-
Night sweats	1 (1)	-	3 (4)	-	-	-

Abbreviations: AE - adverse event; BAT - best available therapy.
For the fedratinib arm, only participants who initially were randomly assigned to fedratinib are included. For crossover participants in BAT arm, only data before crossover are included.

3.4.6 AEs of special interest

AEs of special interest (AESIs) are shown in Table 19 and reported in the company's clarification response (question A27).[17] The most common AESIs in the fedratinib arm were anaemia (32%), cardiac failure/cardiomyopathy (28%), thrombocytopenia (27%), thiamine levels below normal (20%) and peripheral oedema (19%). In the BAT group (no crossover), the most common AESIs were anaemia (21%), cardiac failure/cardiomyopathy (12%) and peripheral oedema (10%).

Transformation to AML was reported to occur in 1 patient in the fedratinib group and 1 patient in the fedratinib crossover group.

The study protocol (Section 1.3) notes that in November 2013 all fedratinib studies were placed on clinical hold by the United States Food and Drug Administration (U.S FDA) due to preliminary data on fatal and serious cases of Wernicke's encephalopathy and heart failure. In total, 8 potential cases of Wernicke's encephalopathy were identified among 807 patients and healthy trial subjects. No cases were identified with a fedratinib dose of 400 mg or lower. The cases were found to have considerable

predisposing factors. Cases were likely to be related to thiamine deficiency linked to use in a population with poor nutrition and gastrointestinal AEs. The U.S. FDA removed the clinical hold in August 2017. Since then, risk mitigation for Wernicke's encephalopathy was required in the form of routine thiamine monitoring and supplementation, and use of a daily fedratinib dose of 400 mg. In FREEDOM-2, Wernicke's encephalopathy occurred in 1 patient (0.7%) in the fedratinib group, while "encephalopathy including Wernicke's" occurred in 22% and 7% in the fedratinib and fedratinib crossover groups respectively and in 4% in the BAT group.

Table 19: FREEDOM-2: AEs of special interest (AESIs) (adapted from company's clarification response, Tables 8 and 9)

	AESIs: N (%)			**Treatment-related AESIs: N (%)**		
	Fedratinib (N=134)	**Fedratinib crossover (N=46)**	**BAT (N=67)**	**Fedratinib (N=134)**	**Fedratinib crossover (N=46)**	**BAT (N=67)**
Subjects with at least 1 AESI	107 (80)	28 (61)	29 (43)	57 (43)	19 (41)	9 (13)
Grade 3 or 4 Anaemia	44 (33)	13 (28)	14 (21)	13 (10)	8 (17)	6 (9)
Anaemia	43 (32)	13 (28)	14 (21)	13 (10)	8 (17)	6 (9)
Haemoglobin decreased	1 (0.7)	-	-	-	-	-
Cardiac Failure/Cardiomyopathy	38 (28)	6 (13)	8 (12)	3 (2)	2 (4)	1 (1.5)
Oedema peripheral	26 (19)	6 (13)	7 (10)	2 (1.5)	2 (4)	1 (1.5)
Cardiac failure	6 (4)	-	1 (1.5)	-	-	-
Ascites	5 (4)	-	1 (1.5)	1 (0.7)	-	-
Cardiac failure congestive	3 (2)	-	-	-	-	-
Peripheral swelling	3 (2)	-	1 (1.5)	-	-	-
Ejection fraction decreased	2 (1.5)	-	-	-	-	-
Cardiomyopathy	1 (0.7)	-	-	-	-	-
Hypervolaemia	1 (0.7)	-	-	-	-	-
Pulmonary congestion	1 (0.7)	-	-	-	-	-
Pulmonary oedema	1 (0.7)	-	-	-	-	-
Right ventricular dysfunction	1 (0.7)	-	-	-	-	-
Right ventricular failure	1 (0.7)	-	-	-	-	-
Stress cardiomyopathy	1 (0.7)	-	-	-	-	-
Grade 3 or 4 Thrombocytopenia	36 (27)	12 (26)	5 (7)	23 (17)	9 (20)	3 (4)
Thrombocytopenia	36 (27)	12 (26)	5 (7)	23 (17)	9 (20)	3 (4)
Encephalopathy, Including Wernicke's	29 (22)	3 (7)	3 (4)	15 (11)	1 (2)	-
Dysgeusia	5 (4)	1 (2)	-	4 (3)	1 (2)	-
Peripheral sensory neuropathy	5 (4)	-	1 (1.5)	3 (2)	-	-
Amnesia	3 (2)	-	-	3 (2)	-	-
Paraesthesia	3 (2)	1 (2)	-	-	-	-
Confusional state	2 (1.5)	-	-	-	-	-
Herpes zoster	2 (1.5)	-	1 (1.5)	1 (0.7)	-	-
Hypoaesthesia	2 (1.5)	-	-	2 (1.5)	-	-
Vision blurred	2 (1.5)	-	-	1 (0.7)	-	-
Burning sensation	1 (0.7)	-	-	-	-	-
Delirium febrile	1 (0.7)	-	-	-	-	-
Epilepsy	1 (0.7)	-	-	-	-	-
Memory impairment	1 (0.7)	-	-	-	-	-
Metabolic encephalopathy	1 (0.7)	-	-	-	-	-

	AESIs: N (%)			Treatment-related AESIs: N (%)		
	Fedratinib (N=134)	**Fedratinib crossover (N=46)**	**BAT (N=67)**	**Fedratinib (N=134)**	**Fedratinib crossover (N=46)**	**BAT (N=67)**
Post-herpetic neuralgia	1 (0.7)	-	-	-	-	-
Taste disorder	1 (0.7)	-	-	-	-	-
Wernicke's encephalopathy	1 (0.7)	-	-	1 (0.7)	-	-
Bradyphrenia	-	-	1 (1.5)	-	-	-
Febrile convulsion	-	-	1 (1.5)	-	-	-
Peripheral sensorimotor neuropathy	-	1 (2)	1 (1.5)	-	-	-
Thiamine levels below normal range with or without signs or symptoms of Wernicke's encephalopathy	27 (20)	6 (13)	3 (4)	18 (13)	8 (9)	-
Vitamin B1 decreased	17 (13)	4 (9)	2 (3)	11 (8)	2 (4)	-
Vitamin B1 deficiency	10 (7)	2 (4)	1 (1.5)	7 (5)	2 (4)	-
Grade 3 or 4 ALT, AST, or Total Bilirubin Elevation	12 (9)	-	1 (1.5)	5 (4)	-	-
Alanine aminotransferase increased	6 (4)	-	-	5 (4)	-	-
Ascites	3 (2)	-	-	-	-	-
Aspartate aminotransferase increased	2 (1.5)	-	-	1 (0.7)	-	-
Gamma-glutamyltransferase increased	2 (1.5)	-	-	1 (0.7)	-	-
Hepatosplenomegaly	1 (0.7)	-	-	-	-	-
Liver function test abnormal	1 (0.7)	-	-	-	-	-
Portal hypertension	1 (0.7)	-	-	-	-	-
Varices oesophageal	1 (0.7)	-	-	-	-	-
Blood bilirubin increased	-	-	1 (1.5)	-	-	-
Secondary Malignancies	10 (7)	3 (7)	3 (4)	1 (0.7)	1 (2)	1 (1.5)
Squamous cell carcinoma	4 (3)	1 (2)	2 (3)	-	-	1 (1.5)
Squamous cell carcinoma of skin	4 (3)	2 (4)	1 (1.5)	1 (0.7)	1 (2)	-
Adenocarcinoma gastric	1 (0.7)	-	-	-	-	-
Adenocarcinoma of colon	1 (0.7)	-	-	-	-	-
Basal cell carcinoma	1 (0.7)	-	-	-	-	-
Malignant melanoma	1 (0.7)	-	-	-	-	-
Penile cancer	1 (0.7)	-	-	-	-	-
Renal neoplasm	1 (0.7)	-	-	-	-	-
Transformation to AML	1 (0.7)	1 (2)	-	-	-	-
Adrenal neoplasm	-	-	1 (1.5)	-	-	-
Grade 3 or 4 Hyperamylasemia or Hyperlipasemia	7 (5)	1 (2)	2 (3)	3 (2)	-	-
Ascites	3 (2)	-	-	-	-	-
Abdominal pain	2 (1.5)	1 (2)	-	1 (0.7)	-	-
Abdominal pain upper	2 (1.5)	-	1 (1.5)	1 (0.7)	-	-
Nausea	2 (1.5)	-	-	2 (1.5)	-	-
Blood bilirubin increased	-	-	1 (1.5)	-	-	-
Secondary Malignancies - Progression to AML	1 (0.7)	1 (2)	-	-	-	-
Transformation to AML	1 (0.7)	1 (2)	-	-	-	-

Abbreviations: AE - adverse event; ALT - alanine aminotransferase; AML - acute myeloid leukaemia AST - aspartate aminotransferase; BAT - best available therapy.

For the fedratinib arm, only participants who initially were randomly assigned to fedratinib are included. For crossover participants in BAT arm, only data before crossover are included.

3.5 Indirect comparisons

The company states that, because FREEDOM-2 is a head-to-head study including a comparison with BAT, no indirect comparisons or mixed treatment comparisons are included in the submission for FREEDOM-2 (CS Section B.2.9).[2] The CS Appendix D.1.4 includes details of an indirect comparison used within the original submission (TA756). At that time, there was no RCT of fedratinib vs. BAT in a post-ruxolitinib population, so the company undertook an indirect comparison using the single-arm JAKARTA-2 study of fedratinib versus the BAT arms from two studies (the PERSIST-2 RCT[22] of pacritinib vs. BAT and the SIMPLIFY-2 RCT[23] of momelotinib vs. BAT). However, the company notes that this indirect comparison is no longer required for the current submission, so it is not discussed further in this EAG report.

The EAG agrees that no indirect comparison is required for a comparison versus BAT, but notes that an indirect comparison would be required in order to compare against momelotinib; however, no comparison against momelotinib is presented in the CS (see Section 2.3.3).

3.6 Conclusions of the clinical effectiveness section

Methods of systematic review: The company's systematic review has not been updated since February 2020. The EAG considers that the systematic review should have been updated, but agrees that the FREEDOM-2 head-to-head RCT would likely remain the most appropriate study for comparing fedratinib vs. BAT. However, the company has not presented any comparison against momelotinib; such a comparison would likely require an updated systematic review and an indirect comparison.

Clinical evidence: The CS presents data from the FREEDOM-2 RCT of fedratinib vs. BAT and the SACT dataset of fedratinib in the CDF population, both in myelofibrosis patients with prior ruxolitinib. In FREEDOM-2, at EOC6, spleen volume response rate (SVR ≥ 35%) was 36% for fedratinib vs. 6% for BAT (p<0.0001); symptom response rate (TSS reduction ≥ 50%) was 34% for fedratinib vs. 17% for BAT (p=0.0033); and spleen or symptom response rate (used in the company model) was 52% for fedratinib vs. 19% for BAT (p=not reported). Time-to-event outcomes were confounded by the fact that 69% of the BAT arm crossed over to fedratinib by EOC6. Median durability of spleen volume response was 86 weeks for fedratinib and not estimable for BAT, and median durability of symptom response was 12 weeks for fedratinib and 10 weeks for BAT. Time to treatment discontinuation (used as a proxy for duration of response in the model) was [redacted] weeks for fedratinib and [redacted] weeks for BAT in FREEDOM-2, and 25 weeks for fedratinib in SACT. Median OS was not reached for fedratinib (95% CI: 113 weeks to not estimable) and 125 weeks for BAT in FREEDOM-2, and 67 weeks for fedratinib in SACT. The

EAG agrees with the company that none of the methods for crossover adjustment were appropriate; therefore, it is difficult to draw conclusions about comparative OS for fedratinib versus BAT. The most common AEs in the fedratinib arm were diarrhoea (46%), anaemia (44%), nausea (40%), thrombocytopenia (36%), constipation (22%) and asthenia (20%), and in the BAT group (without crossover) were anaemia (36%), asthenia (24%), thrombocytopenia (18%) and nausea (15%). The HRQoL data (EQ-5D-5L and EORTC QLQ-C30) show similar mean changes from baseline between trial arms up to EOC6, with the crossover from BAT to fedratinib at EOC6 making the data beyond 6 months difficult to interpret.

Key issues relating to clinical evidence: The company's systematic review has not been updated since February 2020, though it is likely that FREEDOM-2 remains the most appropriate study to compare fedratinib versus BAT. Since 69% of patients in FREEDOM-2 crossed over from fedratinib to BAT, it is difficult to compare OS, TTD or durability of response beyond EOC6. Median treatment duration was lower in the SACT database than in FREEDOM-2 and OS outcomes were also more pessimistic, raising concerns about the generalisability of the outcomes from FREEDOM-2 to the population likely to receive treatment in clinical practice.

4 COST EFFECTIVENESS

4.1 EAG's comment on company's review of cost-effectiveness evidence

4.1.1 Objective of cost effectiveness review

The CS states that the purpose of the review of cost-effectiveness studies was to support the development of the *de novo* economic model for fedratinib for TA756.[2] The CS states that an updated review has not been conducted to support this re-appraisal of TA756 and refers to the original review which was conducted in February 2020.[2] The rationale given for not updating the review of cost-effectiveness studies is consistent with the rationale given for not updating the clinical effectiveness reviews which is that, "*no further evidence is anticipated to be found other than the pivotal trial FREEDOM-2 (providing head-to-head data); therefore, an update of the SLR (February 2020) would not affect this submission."*[2]

The CS also describes reviews of HRQoL and resource use literature which are described in detail in CS Appendices H and I.[2] The relevance of these reviews to the company's model is described in the relevant sections below (Section 4.2.5.4 and 4.2.5.5), but the searches are critiqued here alongside the searches for the cost-effectiveness review due to similar issues affecting all three reviews, in particular the lack of updates since February 2020.

4.1.2 Search strategies

Appendices G, H and I of the CS report on the searches as part of the systematic literature review for the following: cost-effectiveness (Appendix G); HRQoL life (Appendix H); cost and health care resource identification, measurement and valuation (Appendix I). The CS reports on the search strategy for searches carried out in February 2020, but it does not include transcripts of individual database searches. These were provided in full as part of the company's clarification response (question B1) for an updated search carried out in April 2021.[17] The EAG's comments in this report are based on the search strategy provided in the CS and the transcripts of the search strings provided in the clarification response. However, given that the EAG is unable to find any reference in the current submission, or in the committee papers for TA756 to searches that were updated in April 2021,[2, 24] the EAG is unclear if these were the searches used to inform the review described in the current submission.

The expected core bibliographic databases (MEDLINE, including MEDLINE In-Process; Embase; EconLit; and both the National Health Service Economic Evaluations Database [NHS EED] and the Health Technology Assessment (HTA) database on the Cochrane Library) were systematically searched. No date limits were applied for MEDLINE In-Process, EconLit, NHS EED and HTA, although it is to be noted that NHS EED and HTA stopped being updated in 2015, so there is an inbuilt cut-off publication date for literature from those sources. The Embase.com search of MEDLINE and

Embase was an update search for literature between the previous search in February 2020 and the time of the search update, April 2021. According to the CS, relevant conference proceedings were searched between 2017 and 2019,[2] but it is unclear from the clarification response whether updated searches of these were run in 2021 in line with the updated database searches.

There are six search strings reported: a combined embase.com search of MEDLINE and Embase for each of the three economic evaluation areas of interest (economic evaluation; cost and resource use; utility); a combined search for all three study types on each of the remaining databases (Medline In-Process; EconLit; Cochrane for NHS EED and HTA). For each of these, the number of results per search line is recorded, although the EAG has not been able to replicate exactly the searches run on embase.com.

The search strategies themselves have generally been logically devised and make use of both subject headings and free-text search terms. However, as with the clinical searches (critiqued in 3.1.1), the same search string seems to have been used for Embase and Medline, without adapting the subject headings for the specialised Emtree and MeSH thesauri accordingly.

As with the clinical searches (critiqued in 3.1.1), a publication language limit of English-language-only has been applied to the MEDLINE and Embase search, but this has not been explained or justified in the reporting.

Appendix G.1 states that the search strategy was *"adapted from the economic terms recommended by the Scottish Intercollegiate Guidelines Network (SIGN)"*, although the exact nature of the modifications is unclear. The EAG recommends that filters are used in their full tried and tested form, for which they have been validated to work most effectively, to minimise the risk of missing potentially relevant evidence.

4.1.3 The inclusion and exclusion criteria used in the study selection

Appendix G describes inclusion and exclusion criteria, for the review of published economic evaluations, which the EAG consider to be broadly appropriate. The EAG notes that the review did not specify particular interventions or comparators and was therefore seeking to identify economic evaluations of any drug to treat myelofibrosis in patients with intermediate and high-risk myelofibrosis (or indeterminate/undescribed risk). The EAG notes that the inclusion criteria stated no restriction by country, and as such, the review included non-UK studies. The company's response to clarification question B2,[17] states that a Canadian Agency for Drugs and Technologies in Health (CADTH) evaluation of fedratinib[25] published in June 2021, was excluded because, "*Studies published in other countries are not included as the submission focuses on NICE and studies focusing on the UK setting."*

However, this is inconsistent with the fact that the company has included an earlier CADTH evaluation of ruxolitinib,[26] and other non-UK economic evaluations, in its review of published economic evaluations.

4.1.4 Findings of the cost effectiveness review

The company's review identified 9 studies.[7, 26-33] None of these included fedratinib as either an intervention or comparator. Five were economic evaluations conducted to inform HTAs of ruxolitinib, with one being the NICE appraisal of ruxolitinib (TA386),[7] and four being appraisals in other countries.[26, 29, 30, 32] The remaining four were published cost-effectiveness analyses of ruxolitinib in non-UK settings.[27, 28, 31, 33] The main CS document does not discuss the findings of the review, although these are provided in CS Appendix G. EAG does not consider the findings of these studies to be particularly relevant to the current update of TA756 because none provide a comparison of fedratinib against any comparator specified in the scope.

4.1.5 Conclusions of the EAG's critique of the company's cost effectiveness review

The EAG considers that the company's cost-effectiveness review is inadequate because they have failed to conduct any update searches to identify published cost-effectiveness analyses of fedratinib compared any of the comparators specified in the NICE scope. Given that the company's previous review included economic evaluations of ruxolitinib conducted by inform HTAs by both NICE and CADTH, and that review did not restrict studies by country, the EAG considers that the previous appraisal of fedratinib by NICE (TA756)[9] and the cost-effectiveness analysis of fedratinib published by CADTH in 2021[25] would have been identified and included in the review if a recent update had been conducted. It is also possible that other relevant publications exist in the literature that have been missed because the company has not conducted a recent update of the review.

4.2 Summary of the company's submitted economic evaluation

The description of the economic model submitted by the company presented in this ERG report is largely based on information contained within the CS and the revised model submitted in response to the clarification process.[2, 17]

4.2.1 Population

The population for the economic evaluation is described in CS, Table 36 and in line with FREEDOM-2 trial as, *"participants with DIPSS intermediate or high-risk primary myelofibrosis, post-polycythaemia vera myelofibrosis, or post-essential thrombocythaemia myelofibrosis and previously treated with ruxolitinib".*[2] This represents a narrower population than the marketing authorisation (not restricted by ruxolitinib previous use), as mentioned in Section 2.3.1.

Baseline characteristics of the intermediate-2/high risk myelofibrosis patients are based on median and mean values weighted from both treatment arms of FREEDOM-2, and are: median age at baseline 69.3 years, gender distribution 52.2% male, mean weight 69.9 kg, mean body surface area 1.8 m^2. Platelet count distribution was previously used for calculating ruxolitinib required dosage and costs in TA756, but this is no longer used in the current model because the observed distribution of ruxolitinib by daily dose in FREEDOM-2 is used instead as described in Section 4.2.5.5.1.

4.2.2 Interventions and comparators

The intervention is fedratinib 400 mg, taken orally once daily, in line with FREEDOM-2 and the marketing authorisation. The CS base-case assumes fedratinib will be given as per the FREEDOM-2 trial protocol (see Section 4.2.5.1.2), i.e., until disease progression or unacceptable toxicity.[2]

The comparator in the company's model is BAT, which is assumed to consist of a basket of multiple therapies, mainly ruxolitinib, based on the BAT composition in FREEDOM-2 (Table 20). The EAG notes that RBC transfusion was initially modelled only within routine disease management costs. An option to include RBC transfusions within BAT was added as a selectable option within the model in response to clarification (question B5c), but this was not incorporated into the company's updated post-clarification base-case (see Section 4.3.3.10).[17]

For patients who enter the model on fedratinib, upon discontinuation a proportion go on to receive BAT (see Section 4.2.4). The composition of BAT after fedratinib ('subsequent BAT') differs from the BAT received from the start in the BAT comparator arm, as patients cannot receive ruxolitinib as part of subsequent BAT after fedratinib. In addition, a scenario analysis explores the impact of allowing patients who initially responded to fedratinib, to receive fedratinib as part of subsequent BAT after they stop responding to fedratinib (hence called suboptimal fedratinib). However, the company base-case excluded suboptimal fedratinib on the basis that it is, "*highly unlikely to occur in clinical practice because most patients would move onto supportive care after failure of 2 JAKi treatments*".

The EAG notes that this was an area of uncertainty during the previous appraisal of fedratinib, in which the TA756 guidance stated, "*The committee understood that in practice clinicians would likely be reluctant to stop fedratinib even if the disease does not fully respond, or stops responding. This was because there would be no other treatment options. The committee concluded that it was appropriate to assume that 89% of all people starting fedratinib would continue fedratinib after their disease stops responding. This was consistent with the proportion [89%] who were assumed to continue ruxolitinib in the best available therapy arm*."[9] The EAG understands that for the current appraisal, the equivalent scenario would involve 77.6% of patients receiving suboptimal fedratinib, regardless of whether they responded to fedratinib initially and allowing all patients to have BAT after fedratinib rather than a

proportion going straight to supportive care. This is equivalent to the scenario requested in clarification question B8;[17] however, the EAG notes it was unable to replicate the company's results for this scenario. This issue is discussed in detail in Section 4.3.3.2.

Subsequent BAT composition modelled after fedratinib was reweighted to 100% to adjust for the exclusion of ruxolitinib (Table 20). Additionally, the CS base-case assumes a RDI of 96.7% for fedratinib equivalent to median RDI observed in the all-treated fedratinib arm.[2] Ruxolitinib costs were calculated based on the doses received in different cycles (Section 4.2.5.5.1), so an RDI for ruxolitinib was not included. An RDI of 100% was assumed for all other treatments (clarification response to question B38).[17]

Table 20: Composition of BAT in the company's base-case and its scenario analysis including all drugs (sourced from clarification response to questions A12 & B6 and company's post-clarification model)

Treatment	BAT composition as per FREEDOM-2 (N=67) Number (proportion)[a]	Company's base-case[b]		Company's scenario analysis including all drugs[c]	
		BAT composition as a comparator	BAT composition after fedratinib[d]	BAT composition as a comparator	BAT composition after fedratinib[d]
Ruxolitinib	52 (77.6%)	77.6%	0%	77.6%	0%
Danazol	1 (1.5%)	1.5%	16.7%	1.5%	2.4%
Hydroxycarbamide	1 (1.5%)	1.5%	16.7%	1.5%	2.4%
Interferon alfa	1 (1.5%)	1.5%	16.7%	1.5%	2.4%
Prednisolone	1 (1.5%)	1.5%	16.7%	1.5%	2.4%
Prednisone	1 (1.5%)	1.5%	16.7%	1.5%	2.4%
Thalidomide	1 (1.5%)	1.5%	16.7%	1.5%	2.4%
Fedratinib	0 (0%)	0%	0%	0%	0%
Treatments added to the company's updated model post-clarification in a scenario analysis					
RBC transfusion	19 (28.4%)	0%	0%	28.4%	46.3%
Hydroxyurea	12 (17.9%)	0%	0%	17.9%	29.3%
No treatment	2 (3.0%)	0%	0%	3.0%	4.9%
Mercaptopurine	1 (1.5%)	0%	0%	1.5%	2.4%
Methylprednisolone	1 (1.5%)	0%	0%	1.5%	2.4%

[a] *Company clarification response to question A12*[17]
[b] *Company clarification response to question B6*[17]
[c] *Extracted from the post-clarification model by the EAG*
[d] *Reweighting is applied to redistribute patients receiving ruxolitinib to other treatments included in BAT; for the company's scenario analysis this included the full list of treatments used in BAT in FREEDOM-2*

4.2.3 Perspective, time horizon and discounting

The company's economic analysis is described in the CS as taking an NHS and Personal Social Services (PSS) perspective (CS, Table 40).[2] The CS base-case uses a time horizon of 30 years to cover the remaining lifetime of all sampled patients included in the model. The company's model discounts future costs and benefits at 3.5% per annum.

4.2.4 Model structure

The economic model submitted by the company is built via Visual Basic for Applications (VBA) in Microsoft Excel® and uses an individual patient-level discrete event simulation whereby 10,000 patients are sampled in the CS base-case. Figure 13 depicts the company model structure and comprises four mutually exclusive health states; (a) on JAK inhibitor, (b) on BAT, (c) Supportive care, and (d) Death.

The same patients are sampled to experience both treatment pathways. Every patient is assumed to have the median age and mean weight as described in Section 4.2.1. Each patient is sampled a gender (male or female), time to death using general population mortality life tables, and response to fedratinib or BAT when received first (responder or non-responder).

The patient's response to initial treatment (fedratinib or BAT), determines both the utility values a patient gets while on treatment, where responders have higher values than non-responders (see Section 4.2.5.4), and the likelihood of getting subsequent BAT after fedratinib, where responders are more likely to receive BAT. It is worth noting that for any given patient in the patient-level simulation, the same random number sample is used to assign response to fedratinib, when simulating outcomes for fedratinib, and response to BAT when simulating outcomes for comparator BAT, rather than sampling response to each independently. Hence any patient simulated as a responder to BAT is also simulated as a responder to fedratinib because of the higher response rate observed on average across the fedratinib arm in FREEDOM-2 (Sections 3.3.1 and 4.2.5.2). Additionally, the model's VBA code allows a choice of parametric curves to be used to sample TTD and death conditional on response; however, these were assumed to be the same among responders and non-responders in the CS base-case (Sections 4.2.5.1.1 and 4.2.5.1.2). This means that there is no survival gain assumed to be associated with fedratinib compared to BAT.

Patients enter the model either in the 'on JAK inhibitor' state for the fedratinib arm or the 'on BAT' state for the BAT arm. Upon model entry, each patient is assigned a sampled TTD from the selected parametric survival model (as described in Section 4.2.5.1.2), and time to death from the selected parametric survival model (as described in Section 4.2.5.1.1) using the same random number. This means that sampled TTD and OS are correlated, whereby patients who are sampled longer time on treatment are sampled longer time to death, and vice versa.

The sampled time to death is compared to the one sampled from general population mortality life tables, and the earlier time is selected for the patients. Patients are assumed to die while on treatment if time to death sampled from the life tables is shorter than their sampled TTD.

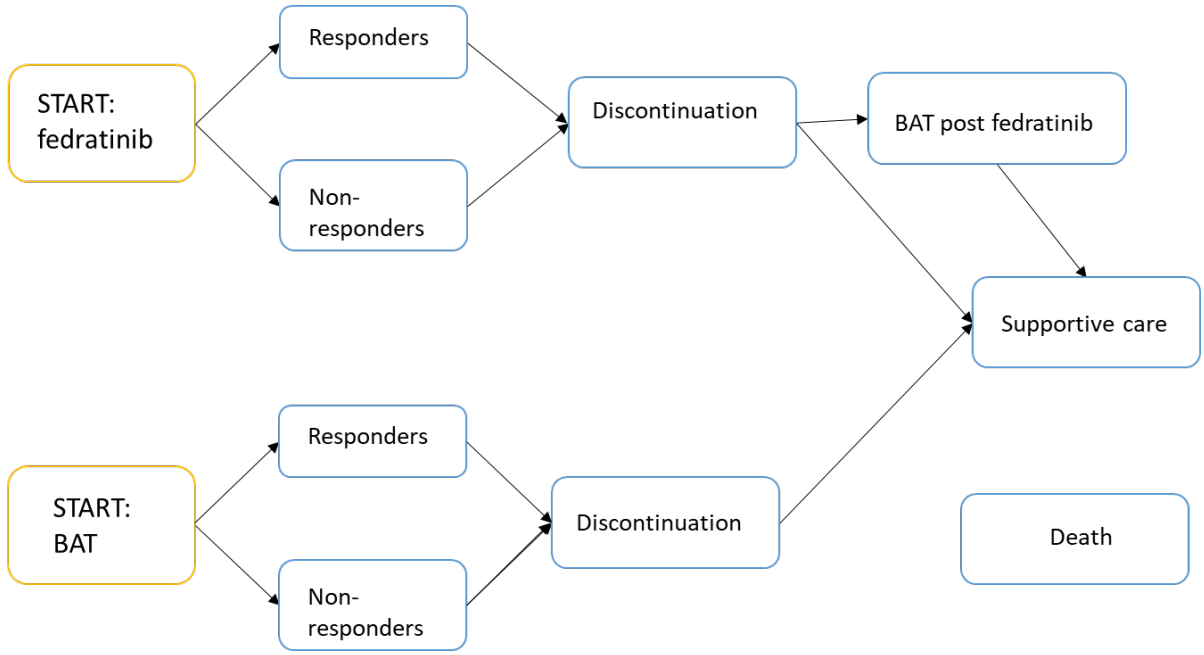
Patients who discontinue treatment (either fedratinib or BAT) and could either go to the 'on BAT' state after fedratinib or the 'supportive care' state after either fedratinib or BAT. 66.7% of responders to fedratinib were assumed to get subsequent BAT compared to 33.3% of non-responders. In response to clarification question B31 asking about these assumptions, the company stated that these transition probabilities were "*informed by inputs from clinical opinion received during the original submission*" and "*not updated as part of the new FREEDOM-2 data*."[17] The EAG could not track these statements down in the committee papers of the original submission and therefore remains uncertain about the clinical plausibility of these assumptions.[24] The EAG did identify that [redacted] patients in the fedratinib arm had at least one systemic anti-cancer therapy after stopping treatment with fedratinib (CSR, Table 14.1.8.3.2),[19] which is [redacted]% of those alive at discontinuation (N=78 discontinued for reasons other than death,

Table 8). The assumptions regarding treatment received after fedratinib is further discussed in Sections 4.3.3.2 and 4.3.3.3.

For patients who get subsequent BAT after fedratinib, no TTD is explicitly modelled. Instead, time on subsequent BAT is determined based on the remaining time to death which is assumed to split to 59.6% on BAT and 40.4% in supportive care, based on the ratio of predicted undiscounted life years (LYs) spent in the BAT and supportive care states in the BAT comparator arm.

Patients who enter the 'Supportive care' state remain there until death. After death, undiscounted and discounted outcomes in terms of costs and QALYs are calculated for each patient based on the amount of time spent in each alive health state.

Figure 13: Structure of the economic model



The EAG notes that this model structure differs from the one submitted by the company in the previous appraisal,[34] notably in three domains: (a) duration of response is not sampled separately, instead patients are assumed to respond until treatment discontinuation, (b) exclusion of the 'acute myeloid leukaemia' state and (c) replacement of the 'palliative care' state in the final 8 weeks of life by 'supportive care' state where patients spend the rest of their lives after discontinuing fedratinib or BAT.

In summary, the company's model employs the following key assumptions for its base-case:

- OS and TTD are both assumed not to differ between the fedratinib and BAT treatment arms;
- OS and TTD are both assumed not to differ between responders and non-responders;
- The basket of multiple therapies received in the BAT arm of FREEDOM-2, including a high proportion receiving suboptimal ruxolitinib, is assumed to be representative of the treatments likely to be received in clinical practice;
- After discontinuation of fedratinib or BAT, patients no longer receive any JAK inhibitors (there is an option to allow suboptimal fedratinib as a scenario analysis);
- The subsequent BAT composition for patients who get BAT after fedratinib was the same as the BAT used in the comparator arm, with the exclusion of ruxolitinib;
- Ruxolitinib received in the BAT comparator arm was costed based on the dose distribution observed within the first six treatment cycles in FREEDOM-2. The costing assumed that a full cycle of ruxolitinib treatment is dispensed at the start of each cycle and if a patient switches doses

within a cycle, both the remainder of the old dose, and the remainder of the new dose after finishing the cycle, were assumed to be wasted;

- The RDI for fedratinib from FREEDOM-2 was used, however 100% RDI was assumed for all other treatments comprising BAT (except ruxolitinib as described in the previous bullet point);
- The proportion of patients receiving subsequent BAT is higher in fedratinib responders than non-responders (66.7% versus 33.3%), with the remainder transitioning straight to supportive care;
- After fedratinib, patients getting subsequent BAT are assumed to spend 59.6% of their remaining life expectancy receiving BAT, and the other 40.4% receiving supportive care;
- Non-responders to BAT are assumed to have zero utility gain from baseline even though a utility gain from baseline is applied to non-responders to fedratinib;
- Only grade ≥3 non-haematological AEs were explicitly included in the company's model;
- Haematological AEs such as thrombocytopenia, anaemia and neutropenia were assumed to be common, and their impact on costs and utilities was assumed to be captured in resource utilisation, applied according to treatment received, and health state utility values, applied according to response;
- AML was modelled as an AE and was assumed to be equivalent across both treatment arms.

4.2.5 Evidence used to inform the company's model parameters

Table 21 summarises the evidence sources used to inform the model's parameters in the company's updated base-case analyses following the clarification process. These are discussed in detail in the subsequent sections.

Table 21: Summary of evidence used to inform the company's base-case analyses

Parameter group	Source
Patient characteristics (age, BSA, weight, proportion of females)	Based on characteristics of trial participants in FREEDOM-2.
OS – both arms	A Weibull model fitted to OS data pooled across fedratinib and BAT treatment groups from FREEDOM-2.
TTD – both arms	A log-logistic model fitted to TTD data pooled across fedratinib and BAT treatment groups from FREEDOM-2.
Response rates at 24 weeks	SVR of ≥35% to indicate spleen response or symptom response of ≥50% reduction in TSS using the MFSAF version 4.0. Both were reported in FREEDOM-2.
HRQoL	MF-8D data collected in FREEDOM-2 used for sourcing baseline utility value, and increments applied to responders and non-responders. Adjustments were sourced from the literature for declining utility in the supportive care state, and an adjustment over time for declining utility with age in the general population based on EQ-5D-3L.
Frequency of AEs	Calculated AE annual incidence rates for either treatment arm based on Grade ≥3 non-haematological AEs from FREEDOM-2. AML rates were sourced from COMFORT-II.
QALY loss resulting from AEs	Estimated disutility per AE was taken from a range of sources. The duration for each AE was assumed 4 weeks. QALY losses therefore only differ between arms due to differing annual incidence rates of AEs.
Drug acquisition costs	MIMS (Monthly Index of Medical Specialities), electronic Market Information Tool (eMIT), and British National Formulary (BNF).[35-37]
Disease management costs	Based on different literature sources as detailed in Sections 4.2.5.5.3 and 4.2.5.5.4.
Costs associated with AEs	Based on different literature sources as detailed in Section 4.2.5.5.5.
End of life care costs	Based on Round *et al*,[38] inflated to 2022 costs using the HCHS pay & prices and the NHSCII indices.[39]

Abbreviations: AE - adverse event;AML - acute myeloid leukaemia; BSA - body surface area; CSP - combined positive score; EQ-5D-3L - EuroQol EQ-5D 3-level; HCHS - hospital & community health services; HRQoL - health-related quality of life; KM - Kaplan-Meier; NHSCII - NHS Cost Inflation Index; OS - overall survival; QALY - quality-adjusted life year; SVR - spleen volume reduction; TSS - total symptom score; TTD - time to treatment discontinuation.

4.2.5.1 Time-to-event parameters

Patient-level data from FREEDOM-2 were used to fit parametric survival models for two time-to-event outcomes used to inform the economic model: OS and TTD.

The observed OS and TTD in FREEDOM-2 were considered to be similar across treatment groups (Figure 5 and Figure 8) and formal adjustment for treatment switching was not considered to be appropriate (see Section 3.3.9). The company's base-case therefore assumes that there is no difference according to treatment arm and uses data pooled across fedratinib and BAT treatment groups. These main analyses are summarised below in Section 4.2.5.1.1 for OS and Section 4.2.5.1.2 and TTD. The

company also conducted several different scenario analyses, which are further summarised and critiqued in Section 4.3.3.14. These included exploring analyses that modelled OS and TTD separately by treatment group and analyses that modelled OS and TTD separately for responders and non-responders within each treatment group.

For all analyses, the company fitted six standard parametric survival models (exponential, Gompertz, log-logistic, log-normal, Weibull, and generalised gamma distributions). Model fit was assessed based on the Akaike information criterion (AIC) and the Bayesian information criterion (BIC). Visual inspection and plausibility of the extrapolations were also considered in the company's final model selection. Plausibility for OS was based on an advisory board with 5 clinical experts who provided estimates of OS at 2, 5, 10 and 20 years (CS Appendix M). Assessment of the proportional hazards (PH) and accelerated failure time (AFT) assumptions for models with covariates did not inform the original model selection in the CS. The EAG requested this at clarification (question B14) and the company provided assessment of the PH assumption based on log-cumulative hazards plots and Schoenfeld residuals, but the AFT assumption was not assessed.[17] The EAG also requested non-parametric estimates of the hazard functions for OS and TTD but these were not provided with the above-mentioned response, with the company stating that "*given the small sample size, it was judged that hazard estimates would be too noisy to be informative*".[17]

4.2.5.1.1 Overall survival (OS)

The company's base-case considered data pooled across the treatment groups. Model fit to the observed data and the company's model selection process is summarised in

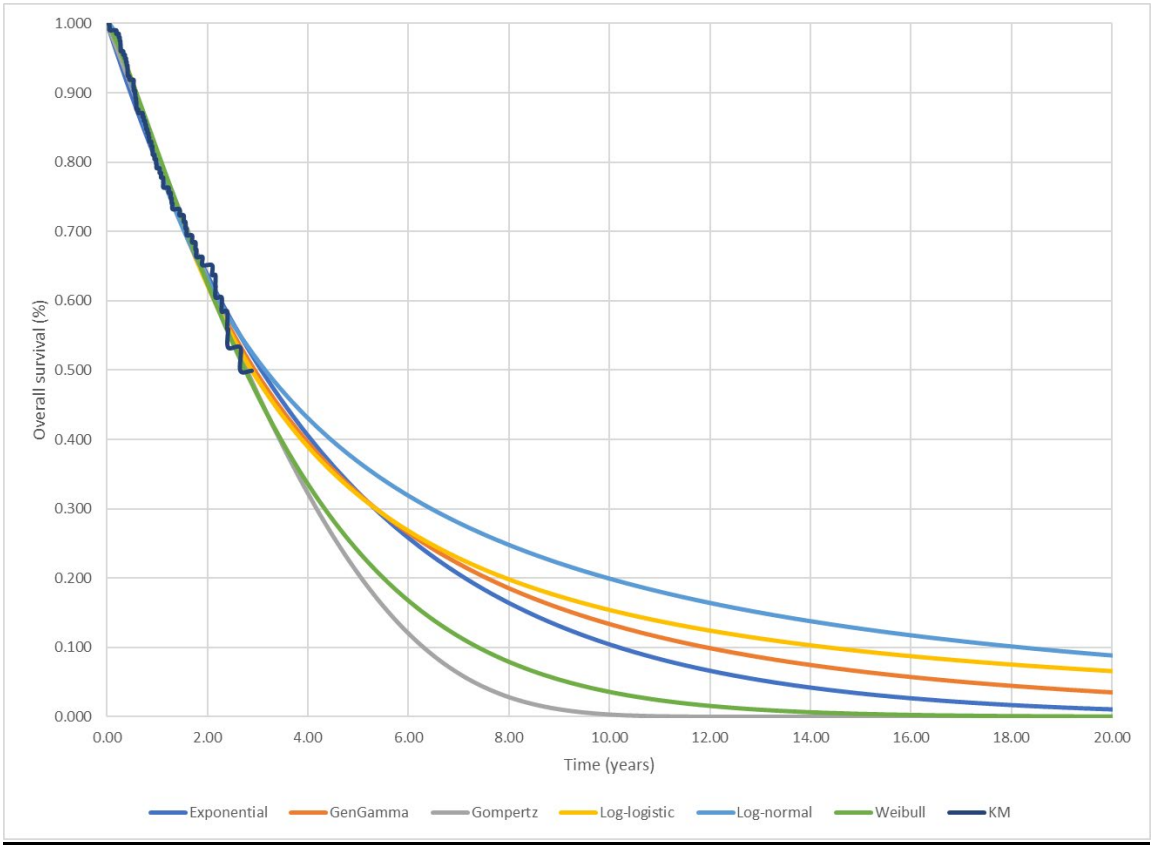
Table 22 and the fitted survival curves are plotted in Figure 14. Although the log-logistic model provided a good fit to the observed data based on AIC and BIC, the predicted 20-year survival probability of 7% was considered an over-estimate, based on clinical advice that survival was likely to reduce to 0% within 20 years. The generalised gamma and log-normal models were also ruled out for this reason. The Weibull model was selected for the base-case and Gompertz was also considered in model scenario analyses.

Table 22: Summary of parametric model selection for OS (adapted from CS Tables 48 & 49)

Model	AIC	BIC	20-year survival probability*	Overall judgement
Exponential	[redacted]	[redacted]	1%	Constant hazard considered implausible
Generalised gamma	[redacted]	[redacted]	4%	Overestimates long term survival
Gompertz	[redacted]	[redacted]	0%	**Chosen for scenario analysis**
Log-logistic	[redacted]	[redacted]	7%	Overestimates long term survival
Log-normal	[redacted]	[redacted]	9%	Overestimates long term survival
Weibull	[redacted]	[redacted]	0%	**Chosen for base-case**

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion
** Modelled survival probability summarised from CS Table 48[2, 17]*

Figure 14: OS for pooled fedratinib/BAT (base-case uses Weibull)



BAT - best available therapy; KM - Kaplan-Meier.

4.2.5.1.2 Time to treatment discontinuation (TTD)

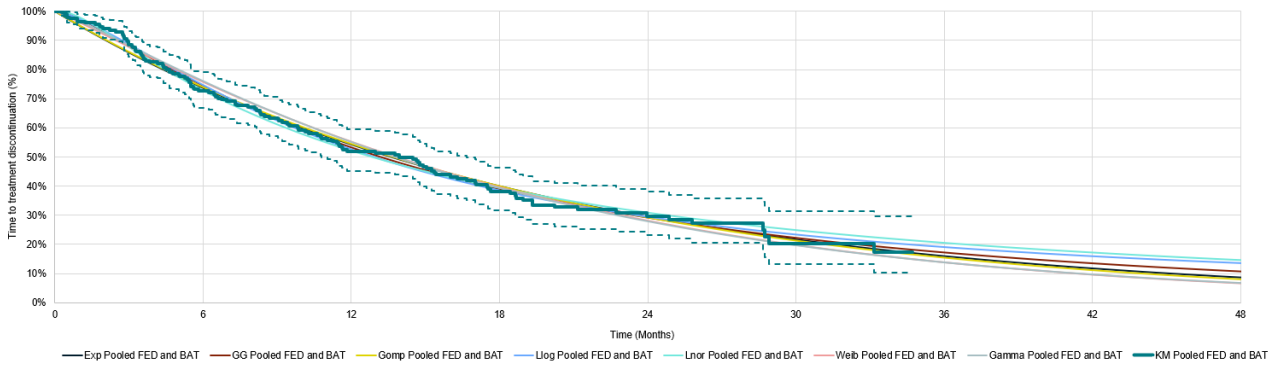
As for OS, the company's base-case considered data pooled over treatment group. Model fit to the observed data and the company's model selection process is summarised in Table 23 and the fitted survival curves for TTD are plotted in Figure 15. The log-logistic distribution was chosen based on visual inspection and model fit based on AIC and BIC. However, there was little difference in fit to the observed data based on AIC and BIC and model extrapolations were similar, with slightly higher TTD for log-logistic and log-normal models towards the end of follow up.

Table 23: Summary of parametric model selection for TTD (adapted from CS Table 50)

Model	AIC	BIC	Overall assessment
Exponential	[redacted]	[redacted]	
Generalised gamma	[redacted]	[redacted]	Chosen for scenario analysis
Gompertz	[redacted]	[redacted]	
Log-logistic	[redacted]	[redacted]	**Chosen for base-case**
Log-normal	[redacted]	[redacted]	
Weibull	[redacted]	[redacted]	

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

Figure 15: TTD for pooled fedratinib/BAT (base-case uses log-logistic) (replicated from CS, Figure 40)



BAT - best available therapy; FED - fedratinib; GG - generalised gamma; KM - Kaplan-Meier; TTD - time to treatment discontinuation.

4.2.5.2 Response rate at 24 weeks

In the CS base-case, response rate at 24 weeks is based on both spleen (volume) and symptom response using the MFSAF version 4.0. An SVR of ≥35% was used to indicate spleen response with 48/134

(35.8%) achieving response on fedratinib versus 4/67 (6.0%) on BAT. Symptom response was assessed via ≥50% reduction in total symptom score (TSS). This occurred in 43/126 (34.1%) patients on fedratinib versus 11/65 (16.9%) on BAT.

The company combined both endpoints for response rates to be used in the model as this, "*was strongly recommended as a modelling input by experts at an advisory board, with the rationale that this outcome would be reflective of UK clinical practice given that the SVR and TSS track together*."[2] This results in SVR or TSS response rates of 52.2% (70/134) on fedratinib versus 19.4% (13/67) on BAT as shown in

Table 12.

As stated in Section 4.2.4, in the company's base-case, responding patients were modelled to have higher utilities than non-responders for the duration of their time on treatment. They were also more likely to receive BAT after fedratinib instead of transitioning directly to supportive care. However, they had the same OS and TTD predictions as non-responders.

4.2.5.3 Adverse events

Only grade ≥3 non-haematological AEs were considered in the company's model. Haematological AEs such as thrombocytopenia, anaemia and neutropenia were assumed to be common, and their impact on costs and utilities was assumed to be captured in resource utilisation and health state utility values applied in the model respectively.

The frequency of grade ≥3 non-haematological AEs assumed in the economic model are taken from FREEDOM-2. These were converted into an exposure-adjusted incidence rate per 100 person-years by dividing the number of patients with specified TEAEs by the total exposure time (in years) to the event, and then dividing the result by 100. In patients crossing over to fedratinib, only AEs and treatment exposure time prior to crossover were attributed to BAT. The company used this approach to account for differences in the duration of treatment for fedratinib and BAT, due to the majority of patients in the BAT arm crossing over to fedratinib at 6 months, rather than using the data only from the first 6 treatment cycles (where both comparators were in use). The exposure-adjusted incidence rate was then used to calculate the annual incidence rate.

The annual incidence rates of grade ≥3 AEs assumed in the economic model are summarised in Table 24. These were used to calculated annual management costs (Section 4.2.5.5) and annual disutility (Section 4.2.5.4) associated with AEs. For subsequent BAT after fedratinib, the annual incidence rates were assumed the same as the BAT arm of FREEDOM-2. Transformation to AML was captured as an AE and was assumed to happen at the same rate in both treatment arms, with an annual incidence rate of 2.87% based on COMFORT-II data (4/73 BAT-treated patients developed AML in a mean exposure of 1.94 years).[40] The company stated that this was because no cases of AML were reported in FREEDOM-2 (CS, Section B.3.3.5);[2] however, the EAG notes that there were 2 cases reported (see Table 19). The EAG notes that AML rates applied in the model were erroneously doubled for BAT because the mean years of exposure for fedratinib in FREEDOM-2 (1.09 years) were incorrectly used in place of the mean years of exposure for BAT in COMFORT-II (1.94 years).

Table 24: Annual incidence rate of non-haematological grade ≥ 3 AEs per treatment arm used in the company's base-case model (all except AML rate were estimated from FREEDOM-2; adapted from CS, Table 45)

Adverse event	Fedratinib	BAT
Abdominal pain	1.37%	2.57%
Acute kidney injury	6.32%	2.53%
Alanine aminotransferase increased	4.32%	0.00%
Aspartate aminotransferase increased	1.38%	0.00%
Asthenia	2.80%	2.53%
Atrial fibrillation	1.39%	0.00%
Cardiac failure congestive	2.05%	0.00%
Chronic kidney injury	3.48%	0.00%
Decreased appetite	2.77%	2.53%
Diarrhoea	1.37%	0.00%
Dyspnoea	2.09%	0.00%
Emphysema	1.38%	0.00%
Gastrointestinal haemorrhage	1.37%	0.00%
General physical health deterioration	7.64%	2.53%
Glomerular filtration rate decreased	2.10%	0.00%
Hyperkalaemia	8.00%	0.00%
Hypokalaemia	2.06%	2.56%
Hyponatraemia	1.37%	0.00%
Pneumonia	2.10%	7.62%
Renal failure	2.75%	0.00%
Renal impairment	2.11%	0.00%
Transformation to AML	2.87%	5.02%

Abbreviations: BAT - best available therapy; AML - acute myeloid leukaemia

4.2.5.4 Health-related quality of life

The EAG notes that whilst the CS describes a systematic review for identifying HRQoL studies (CS, Appendix H), this review has not been updated since February 2020 and the HRQoL data in the model are largely informed by new evidence from FREEDOM-2, supplemented by HRQoL estimates from the literature and previous NICE appraisals.

Utility values in the model are determined by a combination of disease-specific utility values based on MF-8D values obtained from the FREEDOM-2 trial, an adjustment sourced from the literature for declining utility in the supportive care state, and an adjustment over time for declining utility with age in the general population based on EQ-5D-3L. Although EQ-5D-5L utility values were collected in FREEDOM-2, these are not used to inform the model as the MF-8D was considered more appropriate (see Section 4.3.3.9 for a further discussion of this issue). All disease-specific utility values are applied as increments relative to the baseline MF-8D utilities from FREEDOM-2, whereas the adjustment for age-related declines in general population utility values are applied as multipliers to the disease-specific utility values, with separate multipliers applied for males and females.

The patient's utility at the start of the model is set equal to the MF-8D baseline utility in the FREEDOM-2 trial, pooled across both treatment groups, and this utility is maintained for the first four weeks. Thereafter, their utility is dependent on their response status and the treatment currently being received. Utility values for non-responders differ between patients receiving fedratinib and patients receiving BAT, whilst those for responders are the same for both. Patients receiving BAT after fedratinib have the same utility values as non-responders receiving BAT at the start of the model (which is the same as baseline utility value). Once patients transition to supportive care, their utility returns to the baseline utility from FREEDOM-2 and an additional utility decrement is then applied for each whole 24-week period spent in supportive care. The utility values applied in the model are summarised in Table 25.

Table 25: Utility parameters applied in the model (adapted from CS Tables 55 and 56)

Utilities	Description	Change from baseline	Source	Absolute utility
Baseline	Baseline value	NA	FREEDOM-2 analysis	0.649
Fedratinib response	Change from baseline, after 4 weeks in state	+0.168	Estimated from FREEDOM-2 by comparing values predicted by regression with baseline values	0.817
Fedratinib non-response	Change from baseline, after 4 weeks in state	+0.052		0.701
BAT response	Change from baseline, after 4 weeks in state	+0.168		0.817
BAT non-response	Change from baseline, after 4 weeks in state	0.000 [a]	Assumption of no change from baseline	0.649
Worsening utility in supportive care	Ongoing 24-weekly decrement in supportive care	−0.025	Ruxolitinib SMC detailed advice document	0.649 - 0.025 x (number of 24-weeks periods in supportive care)

Abbreviations: BAT - best available therapy; JAK - Janus kinase; SMC - Scottish Medicine Consortium.

Notes: Utilities for male and female patients are the same because they are pooled in the model. BAT non-responders are not experiencing any utility increment because this setting is turned off in the base-case.

[a] An option is provided in the model to set this increment to match that applied in responders (+0.052), but this setting is not applied in the company's base-case.

The change from baseline in utility for responders and non-responders is based on a regression analysis conducted on post-baseline MF-8D utility values pooled across both arms of FREEDOM-2. A mixed effect regression model was used by the company and preferred over the MF-8D values observed in the trial as it allows for the inclusion of multiple covariates (including baseline utility) and includes multiple

observations from each individual (clarification response, question B23).[17] The CS states that the company conducted the regression analysis with the aim of producing health utility estimates with as few covariates as possible; their chosen regression model included coefficients only for baseline utility and response status at 6 months.[2, 17] The company conducted regressions using each of the three different definitions of response (spleen response of SVR ≥ 35%, symptom response of TSS reduction ≥ 50%, and either spleen or symptom response), with the company using response defined by either spleen or symptoms in their base-case.

The company provided additional details on the model selection process in response to a clarification request from the EAG (question B22).[17] The company stated that multiple patient characteristics were assessed in exploratory analyses (age, sex, race, ECOG PS, myelofibrosis diagnosis, haemoglobin count, platelet count), with sex and ECOG PS being explored in the regression models due to results showing a possible correlation between these variables and utility.[17] The model including both sex and baseline utility had a non-statistically significant coefficient for sex. The company chose not to use the model including sex stating that, "*the regression models excluding gender [sex] provided the best fit to the data based on lower AIC and BIC statistics*," and the model excluding sex was more parsimonious (company response to question B22).[17] ECOG PS was also not included in the final model for similar reasons. The regression analysis applied in the company's base-case is summarised in Table 26. The equivalent model including sex is also provided for reference as the relevance of this model is further discussed in Section 4.3.3.11.

Table 26: FREEDOM-2: coefficients from the final regression model for each response definition using the MF-8D (adapted from CS Table 53 and clarification response, Table 12)

Coefficient	Coefficient subcategory	Estimate	Standard error	*p*-value
Spleen or symptom response model excluding sex (base-case)				
Intercept	NA	0.371	0.031	<0.001
Baseline MF-8D utility	NA	0.509	0.043	<0.001
Response status	Non-responder	Reference		
	Spleen or symptom responder	0.115	0.018	<0.001
Spleen and/or symptom response model including sex				
Intercept	NA	0.369	0.031	<0.001
Baseline MF-8D utility	NA	0.499	0.044	<0.001
Response status	Non-responder	Reference		
	Spleen and/or symptom responder	0.115	0.018	<0.001
Sex	Female	Reference		
	Male	0.016	0.019	0.398

Abbreviations: MF-8D - myelofibrosis 8 dimensions; NA - not applicable.

The utility values predicted by the regression model and the summary statistics for the raw values from FREEDOM-2 for responders and non-responders are provided in Table 27. The EAG notes that the regression model predicts absolute utility for responders and non-responders and does not distinguish between patients receiving different treatments. The changes in utility from baseline applied in the model (see Table 25) have then been calculated by comparing these absolute utility values to baseline utility values. So for example, the regression predicts an absolute utility value of 0.701 for non-responders with a baseline utility of 0.649. The utility change from baseline for non-responders is therefore 0.052 (0.701-0.649). However, in the company's base-case model, the gain in utility for non-responders is only applied to those not responding to fedratinib, with zero gain assumed for non-responders to BAT (see Table 25). This difference is driven by an assumption that non-responders to BAT cannot have an improvement in utility, rather than the predictions of the regression analysis (which includes data for both treatment arms and does not differentiate between them). An analysis applying the same utility gain for non-responders in both treatment arms, consistent with the regression model, is provided as an option within the model, but results for this scenario are not presented by the company. This issue of inconsistent utility values been applied for non-responders is further discussed in Section 4.3.3.4. The utility change from baseline for responders has been calculated in a similar manner but has been applied equally to responders to both fedratinib and BAT. Table 27 summarises the absolute values

applied in the model and compares these to the values predicted by the regression and the observed post-baseline MF-8D values from FREEDOM-2 by responder status in FREEDOM-2. The company's base-case model uses the values pooled across sex, but the model includes the option to use sex-specific values for males and females. As this option is discussed further in Section 4.3.3.11, these are also provided in Table 27 for reference.

Table 27: Comparison of disease-specific utility values applied in model and values obtained from FREEDOM-2

Patient category in model	Applied in model	Patient category in analysis of FREEDOM-2 MF-8D utilities	Post-baseline MF-8D from FREEDOM-2, Mean (SD) [a]	Predicted by regression
Utilities pooled across males and females (0.649 at baseline) – company's base-case				
Non-responder (FED)	0.701	Non-responder (pooled across FED and BAT)	0.716 (0.203)	0.701
Non-responder (BAT)	0.649 [b]			
Responder (FED)	0.817	Responder (Pooled across FED and BAT)	0.824 (0.149)	0.817
Responder (BAT)	0.817			
Sex-specific utilities – males (0.711 at baseline)				
Non-responder (FED)	0.790 [c]	Non-responder (pooled across FED and BAT)	0.750 (0.218)	0.740
Non-responder (BAT)	0.711 [b]			
Responder (FED)	0.905 [d]	Responder (Pooled across FED and BAT)	0.858 (0.135)	0.855
Responder (BAT)	0.855			
Sex-specific utilities – females (0.579 at baseline)				
Non-responder (FED)	0.658	Non-responder (pooled across FED and BAT)	0.680 (0.180)	0.658
Non-responder (BAT)	0.579 [b]			
Responder (FED)	0.773	Responder (Pooled across FED and BAT)	0.785 (0.154)	0.773
Responder (BAT)	0.773			

Abbreviations: BAT – best available therapy; FED – fedratinib; MF-8D – Myelofibrosis 8 dimensions
[a] Post-baseline MF-8D values reported of Table 13 of company's response to clarification question B23[17]
[b] EAG prefers to set this value equal to the value predicted by the regression for non-responders
[c] the EAG believes there is an error in the model calculation and this value should be 0.740
[d] the EAG believes there is an error in the model calculation and this value should be 0.855

The EAG notes that the approach of having a health state utility value that declines by 0.025 every 24 weeks for patients receiving supportive care was included in model for TA756 after technical engagement (committee papers for first meeting, page 206, company addendum to NICE submission).[24] A similar approach was previously taken in TA386,[7] and the EAG considers this to be broadly acceptable. Although the CS does not explicitly state the method used to derive the decline in utility of

0.025 per 24 weeks in those receiving supportive care, the EAG believes this to be based on changes in MF-8D data from the COMFORT-I trial. This is based on the cited source being the SMC detailed guidance for ruxolitinib, which describes the utility source for the SMC model as MF-8D values from COMFORT-I and COMFORT-II.[32] Although limited details are given in the SMC document, the CS for the NICE appraisal of ruxolitinib describes using MF-8D values in the placebo arm of COMFORT-I as the source for its estimates of declining utilities in supportive care (although the value itself is redacted in the documents for TA386).[7, 41]

The adjustment for age-declining utilities in the general population is implemented by calculating the ratio of utility for the current age versus utility for the starting age, for each year of the model that the patient is alive, and then applying these as multipliers to ensure that utility declines with age. This was done using age and sex-specific general population EQ-5D-3L utility values for the UK reported by Hernández Alava *et al.*[42] The EAG considered the approach used to adjust for age-dependent decreases in general population utility to be broadly appropriate, but identified a small implementation error in the model whereby the multipliers for females were used for both sexes, which it corrected (see Section 4.3.3.1).

Annual QALY decrements associated with AEs (Table 28) are calculated in the CS from the annual incidence rates of grade ≥3 non-haematological AEs and the disutility associated with the various AEs (CS, Table 58), taken from a range of sources including previous literature, NICE TAs and assumptions. Disutilities were assumed to last 4 weeks except for AML (17 weeks).

Table 28: Annual QALY decrements associated with AEs (extracted from the model)

Treatment	QALY decrement (per year)
Fedratinib	0.008
BAT	0.009
BAT after fedratinib	0.009

Abbreviations: BAT – best available therapy; QALY – quality-adjusted life year

4.2.5.5 Resource use and costs

The following costs categories are included in the company's economic model (CS Section B.3.5):

- drug acquisition and administration costs,
- resource use associated with disease management of myelofibrosis in patients treated with fedratinib, BAT, and supportive care,
- thiamine testing and supplementation for patients on fedratinib,
- costs associated with the management of AEs,
- end-of-life costs.

The EAG notes that whilst the company has described a systematic review for identifying resource use data (see CS, Appendix I), the review has not been updated since February 2020. Resource use in the model is based mainly on literature identified from previous appraisals, with updated unit costs applied or published costs uplifted for inflation.

4.2.5.5.1 Drug acquisition costs

Drug acquisition costs are summarised in Table 29. There is a PAS in place for fedratinib. The discount is [redacted]% leading to a net price of £[redacted] per a pack of 120 tablets (30 days' supply). The weekly cost provided in Table 29 incorporates this PAS. NICE has provided the EAG with a confidential price for ruxolitinib and the impact of including this is explored in a confidential appendix to this report. The cost-effectiveness results when using confidential comparator prices are included in a separate confidential appendix.

The company sourced the drug acquisition costs in the CS from the Monthly Index of Medical Specialities (MIMS) online database, the British National Formulary (BNF) and the Drugs and pharmaceutical electronic Market Information Tool (eMIT) for drugs available in generic form. NICE provided price updates for some of these costs and these have been used in the EAG analyses described in Section 4.4.2.1.

The EAG notes that hydroxyurea and hydroxycarbamide refer to the same drug molecule and should be aggregated; however, the company modelled each separately and applied different unit costs in the model for each of them.

Ruxolitinib is available in four different strengths of 56-tablet packs: 5 mg, 10 mg, 15 mg, and 20 mg. The proportions of patients on different dose strengths used in the company's base-case sum up to 159.5% compared to 77.6% in Table 20. This discrepancy is due to two reasons: (i) patients who are on higher dose strengths than 20 mg are counted twice (i.e., a patient who is on a 25 mg dose would be counted with both 5 mg and 20 mg categories), and (ii) how the company base-case addressed dose switching within treatment cycles and the resulting wastage as discussed below.

Table 29: Drug acquisition costs (adapted from CS, Table 60, with data on additional treatments extracted from the model)

Treatment	Pack size	Unit size	Pack cost	Source	Duration of a pack (weeks)[α]	Weekly cost[†]
Fedratinib	120 tablets	100 mg	[redacted]	Company	4.43[Σ]	[redacted]
Ruxolitinib 5 mg	56 tablets	5 mg	£1,428	MIMS	4.00	£357.00
Ruxolitinib 10 mg	56 tablets	10 mg	£2,856	MIMS	4.00	£714.00
Ruxolitinib 15 mg	56 tablets	15 mg	£2,856	MIMS	4.00	£714.00
Ruxolitinib 20 mg	56 tablets	20 mg	£2,856	MIMS	4.00	£714.00
Danazol	30 capsules	200 mg	£97.64	eMIT	4.29	£22.78
Hydroxycarbamide	100 capsules	500 mg	£10.00	MIMS	4.09	£2.45
Interferon alfa	3 prefilled syringes	3 million IU/0.5 ml	£14.20	MIMS	1	£14.20
Prednisolone	28 tablets	5 mg	£0.30	eMIT	0.67	£0.45
Prednisone	28 tablets	5 mg	£0.94	BNF	2.00	£0.47
Thalidomide	28 capsules	50 mg	£298.48	MIMS	1.00	£298.48
Treatments added to the company's updated model post-clarification in a scenario analysis						
RBC transfusion	1	1	£709.61	NHS Reference costs	4.00	£177.40
Hydroxyurea	25 capsules	50 mg	£14.37	MIMS	0.36	£40.24
No treatment						
Mercaptopurine	25 tablets	50 mg	£8.45	MIMS	1.28	£6.61
Methylprednisolone	20 tablets	100 mg	£48.32	MIMS	9.52	£5.07

Table 30 summarises the company's approach to estimating the dose distribution for ruxolitinib. As patients could have more than one dose of treatment within each cycle, due to dose modifications in response to adverse events, the company used the total count of doses received to estimate the dose distribution. In doing so, each dose contributed once regardless of whether it was given for a full cycle or a single day, resulting in a dose distribution that sums to more than 100%.

Table 30: Dose distribution for ruxolitinib based on doses received across the first 6 cycles (adapted from CS, Tables 61 and 63)

Daily dose received	Count of patients having each dose at any time [a] within each of the first six cycles						Total counts across 6 cycles	Distribution of doses applied base-case [c]
	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6		
2.5 mg								
5 mg								
10 mg								
15 mg								
20 mg								
25 mg								
30 mg								
35 mg								
40 mg								
50 mg								
80 mg								
Sum of doses								
Sum of patients [b]								
Mean dose per patient per cycle assumed in the costing analysis for ruxolitinib								mg

[a] *patients can have more than one dose per cycle due to dose adjustments for adverse events*
[b] *this is based on the number of patients recorded as having an initial dose in each cycle; 52 patients had ruxolitinib within BAT, but only 51 are included in the company's calculations on the 'Ruxolitinib detailed costing' sheet in the model*
[c] *the distribution of doses sums to >100% to allow for multiple doses to be included*

The company's approach assumes that patients receiving more than one dose in each treatment cycle are considered to have used some of these doses with the rest considered as a wastage. For example, a patient switching from 10 mg twice daily to 15 mg twice daily in the middle of a treatment cycle (28 days) was considered to have used half of the 10 mg pack (28 tablets) with the other half being wastage and then used half of the 15 mg pack (28 tablets) with also the other half considered wastage. Overall, this approach led to a considerably higher mean dose (mg) compared to the mean dose observed from the trial (24.1 mg). This issue is further discussed in Section 4.3.3.5.

4.2.5.5.2 Drug administration costs

Oral treatments were assumed to have no associated administration costs. The only injectable, interferon alfa, was assumed to incur a cost of £41.00 per administration, equivalent to a General Practitioner visit where a subcutaneous injection could be administered (company response to question B29). However, the EAG notes that the model option that implements this is not selected in the company's post-classification base-case model and the default value of zero for a self-administered treatment is instead applied.

4.2.5.5.3 Resource use associated with the management of myelofibrosis

Resource use assumed in the CS economic model are summarised in Table 31 and comprise: emergency department visits, blood tests (full blood counts & urea and electrolytes), hospital inpatient stays, hospital outpatient visits, primary care visits, RBC unit transfusion and urgent care visits.

Resource use for each treatment in the CS was derived from: (1) the proportion of JAK inhibitors received (100% fedratinib, 77.6% BAT comparator arm, 0% BAT fedratinib arm), (2) the baseline resource use in the absence of JAK inhibitor (assumed to be constant, see CS Table 66 for details), and (3) relative impact of JAK inhibitor use on resource use (varying with time, see CS Table 67 for details). Resource use for supportive care was assumed equal to BAT except for blood tests and outpatient visits; these were considered to happen at a 50% lower frequency with supportive care than with BAT based on TA386.[7]

Unit costs in the CS are taken from the NHS Reference Costs,[43] Unit Costs for Health and Social Care,[39] Private Patient Tariff (for blood tests)[44] and literature when appropriate (RBC transfusions).[45] Costs were uplifted where appropriate to 2022 values.

Table 31: Costs associated with resource use assumed in the company's base-case (adapted from CS, Table 70)

Cost per week	Fedratinib	BAT as comparator	BAT after fedratinib[a]	Supportive care[a]
0 - 12 weeks	£301.30	£289.70	£249.48	£226.31
12 - 24 weeks	£145.69[b]	£168.93	£249.48	£226.31
24 - 36 weeks	£107.72	£139.46	£249.48	£226.31
36 - 48 weeks	£101.65	£134.74	£249.48	£226.31
48 - 108 weeks	£84.83	£121.69	£249.48	£226.31
108 - 144 weeks	£63.96	£105.50	£249.48	£226.31
144+ weeks	£42.03	£88.47	£249.48	£226.31

[a] *constant over time as the impact of JAK inhibitor on resource use is time dependent and no JAK inhibitor usage is assumed for BAT after fedratinib or supportive care.*
[b] *Reported as £145.96 in CS, Table 70, but here the EAG reports the value directly from the company's model.*

Resource use in the absence of JAK inhibitor therapy is taken from TA386,[7] and was derived from two UK sources: ROBUST[46] and the HMRN audit (2016 and 2020).[6, 47] The impact of JAK inhibitor therapy on resource use relative to BAT (excluding JAK inhibitor use) is derived from JUMP,[48] and similar assumptions to NICE TA386.[7] The three sources mentioned above are as follows:

- HMRN audits: UK audits of clinical management, resource utilisation and outcome in primary and secondary myelofibrosis;
- The ROBUST study: a phase II study that was done in the UK (n=48). It included patients with intermediate-1, intermediate-2 and high-risk disease;

- The JUMP study: A phase III expanded-access trial designed to assess the safety and efficacy of ruxolitinib in patients with high-risk, intermediate-2 risk or intermediate-1 risk disease. This study did not include any patients from the UK.

The EAG notes that there could be issues of double counting in the company's scenario analysis where RBC transfusions are included as part of BAT composition (company's response to clarification question B5c).[17] This issue and other concerns related to the modelling of RBC transfusion are discussed further in Section 4.3.3.10.

4.2.5.5.4 Thiamine testing and supplementation for patients on fedratinib

Additional resource use associated with thiamine testing and supplementation is included in the company's model for patients receiving fedratinib only. Thiamine testing is assumed to occur at baseline, then once every month for the first 3 months, then once every 3 months, and is assumed to be conducted alongside other routine tests meaning no additional outpatient visit is required. A cost of £44 per test is assumed from NHS Reference Costs 2021-22 with 23.13% of patients requiring thiamine based on FREEDOM-2. Patients are assumed to incur thiamine costs continuously until fedratinib discontinuation at an average daily dose of 200 mg. This equates to £4.35 every 7.14 weeks.

4.2.5.5.5 Costs associated with the management of AEs

Unit cost associated with managing AEs (CS, Table 71)[2] in the CS are taken from a multitude of sources including the NHS Reference Costs, Unit Costs of Health and Social Care, assumptions used in TA386 and literature when necessary.[7, 39, 43]

The annual incidence rate of grade ≥ 3 AEs (Table 24**Error! Reference source not found.**) is then multiplied by the respective unit costs (CS, Table 71)[2] to obtain an annual cost for managing AEs (Table 32) in patients treated with fedratinib, BAT (as comparator) and subsequent BAT following fedratinib discontinuation.

Table 32: Annual AE costs (extracted from model by EAG; replaces CS, Table 72 due to updates at clarification)

Treatment	Annual cost
Fedratinib	£2,566
BAT (as comparator)	£3,241
Subsequent BAT (after fedratinib)	£3,241

Abbreviations: BAT - best available therapy

4.2.5.5.6 End-of-life costs

The one-off management cost associated with end of life in the CS is derived from Round *et al* (2015),[38] before being uplifted to 2022 values giving a cost of £6,859 per patient.

4.2.6 Model validation and face validity check

The CS (Section B.3.12) describes a number of measures taken by the company to validate key assumptions in the economic model. The CS states that clinical and health economics experts were sought during the model development to ensure the relevance of inputs and assumptions used in the base-case to the UK clinical practice.[2] However, the EAG is unclear if the company is referring to an advisory board conducted to inform the model submitted for TA756, as the only advisory board report it could identify in the submitted references was dated April 2020.

The CS also describes technical validation by a programmer who was not involved in building the model in terms of reviewing the programming code and assessment of the behaviour of the model results to changes in inputs.[2]

SACT data were also compared to FREEDOM-2 data where worse OS outcomes were observed for fedratinib; however, the median treatment duration was shorter. The company provided a scenario analysis where SACT OS and TTD data were used (see Section 4.3.3.7 for a further discussion of this issue).

4.2.7 Cost-effectiveness results

The probabilistic and deterministic results presented in this section are based on the updated version of the company's model submitted in response to the clarification process (NB: these are provided in the company's post-clarification results document[49] which is separate to the main clarification response[17]). The results presented in this section include the company's agreed PAS discount for fedratinib whilst excluding the PAS discount available for ruxolitinib. The results incorporating the confidential PAS discounts for both fedratinib and ruxolitinib are provided in a confidential appendix to this EAG report.

Results are reported here in terms of incremental net monetary benefit (INMB) for fedratinib versus BAT at a willingness-to-pay (WTP) threshold of £20,000 per QALY gained. The reason for presenting INMBs is that most of the company's analyses were showing fedratinib as the cheaper alternative with more QALYs gained compared to BAT. Incremental cost-effectiveness ratios (ICERs) are also reported for cross-referencing to the updated company base-case results provided in response to clarification.

<u>Central estimates of cost-effectiveness</u>

The company's base-case cost-effectiveness results are presented in Table 33Table 33, which shows the probabilistic estimates of the company's base-case estimated using the average costs and QALYs across 500 probabilistic sensitivity analysis (PSA) samples with 10,000 patients each when the model was re-run by the EAG. Stability charts showed that INMB stabilises after running around 4,000 patients whereas it converged after running the PSA more than 400 iterations.

The probabilistic version of the model suggests that the fedratinib arm is expected to generate an additional [redacted] QALYs with cost savings of £[redacted] per patient compared to the BAT arm, resulting in an INMB of £[redacted] assuming a £20,000 WTP threshold. The deterministic version of the model produces a slightly higher INMB (£[redacted]). The EAG spotted an error with PSA implementation where there was a small difference in life years gained between the two arms which the EAG did not expect given the company's assumption of equivalent OS. Having investigated this, the EAG identified that this was because TTD and OS curve parameters were sampled independently for each treatment and response status for a given PSA run.

Table 33: The company's base-case results (post-clarification)

Technology	LYs	QALYs	Total costs	Incremental			INMB	ICER[a]
				LYs	QALYs	Costs		
Probabilistic model (500 runs by the EAG) [b]								
BAT	[redacted]	[redacted]	[redacted]	-	-	-		Dominant
Fedratinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deterministic model [c]								
BAT	[redacted]	[redacted]	[redacted]	-	-	-		Dominant
Fedratinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BAT, best available therapy; ICER, incremental net monetary benefit; LYs, life years; QALYs, quality-adjusted life years
[a] Dominant indicates that fedratinib has lower costs and higher QALYs than BAT
[b] The company presented probabilistic results for their base-case scenario in Table 7 of the company's post-clarification results document,[49] but the results presented here have been generated by the EAG
[c] Equivalent to results in Table 1 of the company's post-clarification results document[49]

The company's model presents disaggregated outcomes for the deterministic model in terms of costs accrued by different elements and QALYs accrued in different health states. These results are presented in Table 34. The differences in costs are primarily associated with the acquisition cost and how it was calculated for ruxolitinib whilst the additional QALY gain is mainly a consequence of the higher response rates with fedratinib, and the higher utility value associated with response. This is addition to the assumption that non-responders to fedratinib gain higher utility than baseline, whereas non-responders on BAT do not gain any utility relative to baseline.

Table 34: Base-case disaggregated outcomes for company's base-case (deterministic model; adapted from Tables 4, 5 and 6 of company's post-clarification results document)

Description	Fedratinib	BAT	Incremental
Disaggregated costs (discounted)			
Drug acquisition costs of fedratinib	[redacted]	[redacted]	[redacted]
Drug acquisition costs of BAT	[redacted]	[redacted]	[redacted]
Drug administration costs*	[redacted]	[redacted]	[redacted]
Supportive care costs	[redacted]	[redacted]	[redacted]
AE related costs	[redacted]	[redacted]	[redacted]
Disease management costs	[redacted]	[redacted]	[redacted]
Thiamine testing and supplementation	[redacted]	[redacted]	[redacted]
End of life costs	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]
Disaggregated QALYs (discounted)			
On fedratinib	[redacted]	[redacted]	[redacted]
On BAT	[redacted]	[redacted]	[redacted]
On supportive care	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]
Disaggregated LYs (undiscounted)			
On fedratinib	[redacted]	[redacted]	[redacted]
On BAT	[redacted]	[redacted]	[redacted]
On supportive care	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Abbreviations: AE - adverse event; LY - life year; QALY - quality-adjusted life-years.
** The company's updated model introduced an error in their base-case where administration costs for interferon alfa was assumed zero.*

Figure 16 presents the cost-effectiveness plane for the company's base-case PSA, and
Figure 17 shows the corresponding cost-effectiveness acceptability curve (CEAC) (both based on the EAG's re-run of 500 PSA samples). The EAG's re-run of the company's PSA suggests that the probability that the fedratinib arm generates more net monetary benefit than the BAT arm is approximately 1.0, regardless of the ICER threshold. This is a consequence of the predicted cost savings for fedratinib versus BAT.

Figure 16: Company's base-case PSA scatterplot (generated by the EAG)

Figure 17: Company's base-case CEAC (generated by the EAG)

4.2.8 Company's deterministic sensitivity analyses

The company's deterministic sensitivity analyses were re-run by the EAG post-clarification and are presented using a tornado plot using INMBs assuming a £20,000 WTP threshold (Figure 18). The analyses are performed by using the lower and upper bounds of 95% confidence intervals, assuming that the standard error was equal to 10% of the parameter mean if this was not reported. The company's results show that the parameters which had the biggest impact on the INMBs were the probabilities and costs related to transformation to AML and the baseline utility value for females.

Figure 18: One-way scenario analysis results for the company's post-clarification base-case (extracted by EAG)

4.2.9 Company's deterministic scenario analyses

The scenario analyses presented in the company's post-clarification results document are provided in Table 35.[49]

Table 35: Scenario analyses included in the model and their justifications (adapted from Table 9 of company's post clarification results document)

Scenario number	Scenario description	Model settings	Inc costs, £	Inc QALYs	ICER[a], £
1	Base-case	OS (Pooled Fed/BAT): Weibull TTD (Pooled Fed/BAT): Log-logistic Suboptimal fedratinib: 0% Include disutility for AEs and disutility for time spent in supportive care	[redacted]	[redacted]	Dominant [redacted]
2	Maintains base-case assumption that OS equal in fedratinib and BAT (uses pooled Fed/BAT); TTD equal in fedratinib and BAT (uses pooled Fed/BAT); OS and TTD equal for responders and non-responders. OS parametric distribution changed from Weibull to Gompertz	OS distributions assigned: FED OS non-responders: Gompertz FED OS responders: Gompertz BAT OS responders: Gompertz BAT OS non-responders: Gompertz TTD setting as per base-case Other settings as per base-case	[redacted]	[redacted]	Dominant [redacted]

Scenario number	Scenario description	Model settings	Inc costs, £	Inc QALYs	ICER[a], £
3	Maintains base-case assumption that OS equal in fedratinib and BAT (uses pooled Fed/BAT); TTD equal in fedratinib and BAT (uses pooled Fed/BAT); OS and TTD equal for responders and non-responders. TTD parametric distribution changed from log-logistic to gen. gamma	OS distributions assigned: OS settings as per base-case FED TTD responders: gen. gamma FED TTD non-responders: gen. gamma BAT TTD responders: gen. gamma BAT TTD non-responders: gen. gamma Other settings as per base-case	[redacted]	[redacted]	Dominant [redacted]
4	OS and TTD modelled separately by treatment (same across responders and non-responders). Distributions assigned: FED OS: Weibull FED TTD: exponential BAT OS: Weibull BAT TTD: exponential	Distributions assigned: FED OS responders – separated by treatment only: Weibull FED OS non-responders – separated by treatment only: Weibull FED TTD responders – separated by treatment only: exponential FED TTD non-responders – separated by treatment only: exponential BAT OS responders – separated by treatment only: Weibull BAT OS non-responders – separated by treatment only: Weibull BAT TTD responders – separated by treatment only: exponential BAT TTD non-responders – separated by treatment only: exponential Other settings as per base-case	[redacted]	[redacted]	Dominant [redacted]

Scenario number	Scenario description	Model settings	Inc costs, £	Inc QALYs	ICER[a], £
5	OS modelled as per base-case TTD modelled separately across fedratinib and BAT (same across responders and non-responders). Distributions assigned for TTD: FED TTD: exponential BAT TTD: exponential	OS as per base-case TTD distributions assigned: FED TTD responders – separate by treatment only: exponential FED TTD non-responders – separate by treatment only: exponential BAT TTD responders – separate by treatment only: exponential BAT TTD non-responders – separate by treatment only: exponential Other settings as per base-case	[redacted]	[redacted]	Dominant [redacted]
6	OS and TTD modelled as per base-case Does not include AE disutility. Does not include worsening utility on supportive care to both fedratinib and BAT.	All time-to-event settings as per base-case Suboptimal fedratinib: 0% All disutilities associated with AEs set to zero Disutility applied for each 24 weeks spent in supportive care set to zero Other settings as per base-case	[redacted]	[redacted]	Dominant [redacted]
7	BAT modelled using curves fitted to dataset excluding patients with crossover ('No crossover for BAT') BAT OS: Weibull BAT TTD: log-logistic Fedratinib OS and TTD modelled as per base-case (pooled Fed/BAT data)	OS and TTD for fedratinib as per base-case Distributions assigned for BAT: BAT OS responder – no crossover: Weibull BAT OS non-responder – no crossover: Weibull BAT TTD responder – no crossover: log-logistic BAT TTD non-responder – no crossover: log-logistic Other settings as per base-case	[redacted]	[redacted]	[redacted]

Scenario number	Scenario description	Model settings	Inc costs, £	Inc QALYs	ICER[a], £
8	OS and TTD separated only by treatment (as per scenario 4), but different distributions assigned: FED OS: log-normal FED TTD: log-normal BAT OS: Weibull BAT TTD: log-logistic	FED OS responder – separated by treatment only log-normal FED OS non-responder – separated by treatment only log-normal FED TTD responder – separated by treatment only log-normal FED TTD non-responder – separated by treatment only log-normal BAT OS responder – separated by treatment only Weibull BAT OS non-responder – separated by treatment only Weibull BAT TTD responder – separated by treatment only log-logistic BAT TTD non-responder - separated by treatment only log-logistic Other settings as per base-case	[redacted]	[redacted]	Dominant [redacted]
9	OS and TTD are split by treatment and response status. Distributions assigned: FED OS NR: log-normal FED OS R: log-normal FED TTD NR: log-logistic FED TTD R: gen gamma BAT OS NR: Weibull BAT OS R: no crossover: log-normal BAT TTD NR: exponential BAT TTD R: gen gamma	FED OS responder –log-normal FED OS non-responder –log-normal FED TTD responder –gen gamma[c] FED TTD non-responder –log-logistic[c] BAT OS non-responder –Weibull BAT OS responder – no-crossover log-normal BAT TTD non-responder –exponential BAT TTD responder - gen gamma Other settings as per base-case	[redacted]	[redacted]	Dominant [redacted]

Scenario number	Scenario description	Model settings	Inc costs, £	Inc QALYs	ICER[a], £
10	OS and TTD are split by treatment and response status (as per scenario 9) but with different distributions assigned: FED OS NR: Weibull FED OS R: Weibull FED TTD NR: log-normal FED TTD R: log-normal BAT OS NR: log-normal BAT OS R: no crossover: log-normal BAT TTD NR: exponential BAT TTD R: gen gamma	FED OS responder – Weibull[c] FED OS non-responder – Weibull[c] FED TTD responder –log-normal[c] FED TTD non-responder – log-normal[c] BAT OS responder – no-crossover log-normal[c] BAT OS non-responder – log-normal[c] BAT TTD responder – gen. gamma[c] BAT TTD non-responder – exponential[c] Other settings as per base-case	[redacted]	[redacted]	Dominant [redacted]
11	Responder scenario 1: OS is, split by treatment and response status, except BAT responders where pooled FED/BAT data are applied. Distributions assigned: FED OS NR: Weibull FED OS R: Weibull BAT OS NR: log-logistic BAT OS R (pooled FED/BAT): Weibull TTD continues to use pooled FED/BAT Suboptimal fedratinib: 0%	TTD settings as base-case FED OS non-responder - Weibull FED OS responder – Weibull BAT OS non-responder –log-logistic BAT OS responder – pooled Fed/bat Weibull Other settings as per base-case	[redacted]	[redacted]	Dominant [redacted]

Scenario number	Scenario description	Model settings	Inc costs, £	Inc QALYs	ICER[a], £
12	Responder scenario 2: OS is split by treatment and response status, except BAT responders where pooled FED/BAT data are applied. Distributions assigned: FED OS NR: exponential FED OS R: exponential BAT OS NR: log-normal BAT OS R (pooled FED/BAT): exponential TTD continues to use pooled FED/BAT Suboptimal fedratinib: 0%	TTD as per base-case FED OS non-responder - exponential FED OS responder – exponential BAT OS non-responder –log-normal BAT OS responder – pooled Fed/bat exponential Other settings as per base-case	[redacted]	[redacted]	Dominant [redacted]
13	Time-to-event settings as per scenario 11. Suboptimal fedratinib: 32.1%	Time-to-event settings as per scenario 11. Manual input, fedratinib in BAT, after fedratinib (initial responders) 32.1% Fedratinib in BAT Live input 32.1% Other settings as per base-case	[redacted]	[redacted]	Dominant [redacted]
14	Time-to-event settings as per scenario 12 Suboptimal fedratinib: 32.1%	Time-to-event settings as per scenario 12 Manual input, fedratinib in BAT, after fedratinib (initial responders) 32.1% Fedratinib in BAT Live input 32.1% Other settings as per base-case	[redacted]	[redacted]	Dominant [redacted]

Scenario number	Scenario description	Model settings	Inc costs, £	Inc QALYs	ICER[a], £
15	Fedratinib in BAT after fedratinib treatment: 25%	Time-to-event settings as per base-case Fedratinib in BAT for initial responders only Other settings as per base-case	[redacted]	[redacted]	Dominant [redacted]
16	Fedratinib in BAT after fedratinib treatment: 50%	Time-to-event settings as per base-case Fedratinib in BAT for initial responders only Other settings as per base-case	[redacted]	[redacted]	Dominant [redacted]
17	Fedratinib in BAT after fedratinib treatment: 65%	Time-to-event settings as per base-case Fedratinib in BAT for initial responders only Other settings as per base-case	[redacted]	[redacted]	Dominant [redacted]
18	Use of mean dose for ruxolitinib dosing in BAT	Time-to-event settings as per base-case Ruxolitinib cost based on distribution or mean dose: Mean dose Include "additional" wastage for ruxolitinib treatment? (based on TA386 assumptions): Yes Other settings as per base-case	[redacted]	[redacted]	Dominant [redacted]
19[d]	Apply TTD and OS curves fitted to SACT data to both arms	Fedratinib/BAT OS: SACT data - Exponential Fedratinib/BAT TTD: SACT data – Exponential Other settings as per base-case	[redacted]	[redacted]	Dominant [redacted]

[a] *Dominant indicates that fedratinib had lower costs and higher QALYs*

[b] *The EAG obtained an ICER of £[redacted] when it attempted to replicate this scenario*

[c] *This text has been adapted to match the information in the first column of Table 9 in the company's post-clarification results document,[49] as these settings provide ICERs that match the results reported, but the EAG notes that this differs from the text provided in the second column of that table.*

[d] *Scenario reported in response to clarification question B17 and added to this table by EAG.*

4.3 Critique of company's submitted economic evaluation by the EAG

4.3.1 Methods for reviewing the company's economic evaluation and health economic model

The EAG adopted a number of approaches to explore, interrogate and critically appraise the company's economic analyses and the underlying health economic models upon which these are based. These included:

- Scrutiny of the company's model by health economic modellers and discussion of issues identified amongst the members of the EAG.
- Checking the model's programming, including both the Excel spreadsheet calculations and the accompanying VBA coding, to fully assess the logic of the model structures, to draw out any unwritten assumptions and to identify any apparent errors in model implementation.
- Examination of the correspondence between the company's executable models and their description in the CS and the company's response to clarification. [2, 17]
- Replication of the results of the company's base-case, PSA, deterministic sensitivity analyses and scenario analyses reported in the CS and the company's response to clarification.
- Where possible, checking key parameter values used in the company's models against their original data sources.
- Comparison of the model structure and data sources against models used to inform previous NICE appraisals (TA386, TA756 and TA957).[7, 9, 11]
- Examination of the committee considerations for relevant previous appraisals (TA386, TA756 and TA957)[7, 9, 11] and consideration of their likely applicability to the current appraisal.

Some minor errors in the original model were identified by the EAG. These were corrected in the company's updated model submitted in response to clarification (see response to clarification questions B26d, B38d & B38e).[17] In addition, the EAG identified some further minor errors in the post-clarification version of the model, which are described in Section 4.3.3.1. The EAG believes the company's updated version of the model to be generally well programmed despite these errors, and that the version of the model used by the EAG after correcting these errors are appropriate for the decision-making.

4.3.2 Adherence of the company's model to the NICE reference case

The extent to which the company's submission adhere to the NICE Reference Case[50] is summarised in Table 36. The main deviation from the reference case relates specifically to the economic analysis is the use of MF-8D utility values from FREEDOM-2 in preference to EQ-5D utility values which were also available from FREEDOM-2. This is in addition to issues previously discussed in Section 2.3 regarding the omission of momelotinib as a comparator and the CS addressing a narrower population than that specified in the final NICE scope.

Table 36: Adherence of the company's economic analysis to the NICE Reference Case

Element	Reference case[50]	EAG comments
Population	The scope developed by NICE	The population is narrower than that specified in the NICE scope as the CS and economic model focus on people whose disease was previously treated with a JAK inhibitor. This effectively restricts the population to patients with intermediate-2 or high-risk disease due to the wording of the recommendation for ruxolitinib within TA386.[7] The population addressed in the CS is therefore narrower than that specified in the NICE scope, which does not restrict according to treatments received previously or the patient's risk categorisation (see Section 2.3.1).[1]
Intervention	As listed in the scope developed by NICE	Yes, the intervention is fedratinib, given in accordance with its licensed indication, as specified in the NICE scope (see Section 2.3.2). However, time on treatment in the model is based on the fedratinib arm of the FREEDOM-2 study in which patients could only be treated until disease progression. This is in contrast to the SPC for fedratinib stating that it can be continued until, *"lack of therapeutic effect,"*[14] which the EAG considers may include continued use after disease progression. This is termed 'suboptimal fedratinib' and is equivalent to the use of 'suboptimal ruxolitinib' in the BAT arm (see Section 4.2.2).
Comparator(s)	As listed in the scope developed by NICE	No, the model does not provide a comparison against momelotinib (see Section 2.3.3 for a more detailed discussion).
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes, the model captures direct health effects on patients in terms of QALYs. No impacts on carers are included.
Perspective on costs	NHS and PSS	Yes, an NHS and PSS perspective has been adopted with the small exception that the unit costs for blood tests uses a private patient tariff from an NHS hospital.
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	As the company's model only compares fedratinib to BAT, a pair-wise comparison is sufficient. A fully-incremental analysis would be required if momelotinib were added as a comparator, but this would only apply in the subgroup of patients who are eligible to receive momelotinib.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes, a lifetime horizon has been adopted.

Element	Reference case[50]	EAG comments
Synthesis of evidence on health effects	Based on systematic review	The company has not updated its systematic review and has relied solely on outcomes from the FREEDOM-2 study and other sources identified from previous models.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Health effects have been measured using QALYs, with disease-specific utility values determined primarily through the MF-8D measurements obtained from FREEDOM-2. Additional adjustment for age-related declines in utility have been made using general population EQ-5D-3L values. Further adjustments to utilities for declines in utility during time spent in supportive care and AEs have been obtained from the literature. The EAG notes that EQ-5D-5L utility values were available from the FREEDOM-2 trial and a reference case scenario using these values has not been provided by the company despite this being requested during clarification. This issue is further discussed in Section 4.3.3.9. Whilst the EAG considers the use of the MF-8D instead of the EQ-5D to be a deviation from the NICE reference case, there are some similarities between the methods used to obtain valuation sets for the MF-8D and the EQ-5D in that both used a time-trade-off methodology to obtain health state utility valuations from a UK general population sample.[50, 51] This issue is further discussed in Section 4.3.3.9.
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No equity weighting has been applied. The CS states that the conditions required to apply a severity weight were not met in this case.[2]
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	The unit costs applied are appropriate with the exception mentioned earlier of a non-NHS unit cost for blood tests.
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	A discount rate of 3.5% has been applied for both costs and benefits, consistent with the Reference Case.[50]

Abbreviations: BAT - best Available Therapy; CS - company submission; EQ-5D - Euroqol 5-Dimensions; MF-8D - Myelofibrosis 8-Dimension; NHS - National Health Service; PSS - Personal Social Services; QALY - quality-adjusted life year; HRQoL - health-related quality of life; JAK - Janus kinase; SPC - summary of product characteristics; TA - technology appraisal

4.3.3 EAG critique of the modelling performed by the company

The EAG has identified six key issues, within the company's health economic model, which are summarised in Box 1 and described in more detail in Sections 4.3.3.2 to 4.3.3.7. In addition to this, the EAG has identified some minor errors in the company's model, described in Section 4.3.3.1, and a further seven other issues which are described in Sections 4.3.3.8 to 4.3.3.14.

The issues discussed in this section are in addition to those issues already raised previously: a) the lack of a comparison against momelotinib (key issue1, see Section 2.3.3); b) the high proportion of patients crossing over from BAT to fedratinib in FREEDOM-2 making (key issue 2, see Section 3.6); and c) the lack of updated searches to identify health-resource use or quality of life studies to inform the model (see Section 4.1.5).

Box 1: Summary of the main issues identified within the company's health economic model

Key issues

- Uncertainty regarding the composition of BAT received after fedratinib (key issue 3)
- Uncertainty regarding the proportion of patient transitioning straight to supportive care after fedratinib (key issue 4)
- Inconsistent assumptions regarding utility gains in non-responders to fedratinib and BAT (key issue 5)
- Costing of ruxolitinib assumes high wastage due to dose changes (key issue 6)
- Uncertainty regarding duration of suboptimal ruxolitinib within BAT (key issue 7)
- Estimates of OS and TTD from FREEDOM-2 may overestimate the time on treatment and OS expected in clinical practice (key issue 8)

4.3.3.1 Errors identified in the implementation of the model and updates to drug acquisition costs

The EAG identified a number of implementation errors in the updated model version post-clarification:

- In the adjustment for age-related utility declines in the general population, the EAG identified an error, whereby the multipliers for females were used for both sexes (see Section 4.2.5.4).
- In the scenario analysis using sex-specific utility values, the EAG identified an error whereby the changes from baseline for females are applied to the baseline utility for males (see Table 27 and further explanation later in Section 4.3.3.11)
- The AML rates applied in the model were doubled for BAT because the mean years of exposure for fedratinib in FREEDOM-2 (1.09 years) were incorrectly used in place of the mean years of exposure for BAT in COMFORT-II (1.94 years) (see Section 4.2.5.3)

- In response to clarification question B38f) the company did not correct an error related to when discounting starts for supportive care stating that "*some patients can get to the supportive care start as soon as 1 cycle after the model started*".[17] However, the EAG notes that patients can only start on supportive care after discontinuing fedratinib or BAT, and that this statement does not reflect what happens in the model.
- The PSA produced different life-year outcomes because different random numbers were used per treatment and response status to sample the curve parameters for OS and TTD.

In addition, in its pricing tracker form, NICE updated some drug acquisition costs (per pack) using the latest updates from eMIT (Section 4.2.5.5.1). These have been included alongside the corrections to the model errors in the EAG's analyses (see Section 4.4.2.1).

4.3.3.2 Uncertainty regarding the composition of BAT received after fedratinib

It is unclear what proportion of patients will continue to receive suboptimal fedratinib after failing to respond to fedratinib or after initially responding and then later relapsing on fedratinib treatment. The EAG notes that the committee in TA756 stated: "*…in practice clinicians would likely be reluctant to stop fedratinib even if the disease does not fully respond, or stops responding […] because there would be no other treatment options."*[9] It therefore preferred to assume that the proportion receiving suboptimal fedratinib would be the same as the proportion receiving ruxolitinib in the BAT arm. The EAG therefore prefers to assume that 77.6% of people receive suboptimal fedratinib, because this is the proportion receiving suboptimal ruxolitinib in the BAT arm of FREEDOM-2. To achieve the same usage of suboptimal fedratinib in both responders and non-responders it is necessary to assume that 100% of patients receive BAT after fedratinib and 0% go directly to supportive care. Therefore, the EAG applies both these two assumptions together in its preferred base-case (see Section 4.4.2.2).

The EAG notes that allowing patients to have suboptimal fedratinib in the model also addresses the fact that patients were required to stop fedratinib on disease progression in FEEDOM-2, but this is not required in the license where it states fedratinib can be continued until, "*lack of therapeutic effect*."[14] In addition, use of fedratinib in the CDF was allowed "*until loss of clinical benefit*," without any specific requirement to stop on disease progression. Therefore, whilst this assumption extends the duration of time on fedratinib treatment in the model compared to the TTD in FREEDOM-2, this potentially provides better agreement with the use of fedratinib in clinical practice, where treatment is not required to stop on disease progression.

4.3.3.3 Uncertainty regarding the proportion of patients transitioning straight to supportive care after fedratinib

The company's model assumes that some patients transition straight to supportive care after fedratinib treatment rather than receiving subsequent BAT. The proportion transitioning straight to supportive care is assumed to be higher for non-responders to fedratinib and lower for patients who respond initially and then stop responding (66.7% versus 33.3%). In addition, the proportion transitioning to supportive care after stopping BAT is 100%, even in those patients receiving ruxolitinib as part of BAT. This assumption means that the transition to supportive care, which is associated with worsening health utility in the model, is delayed for patients in the fedratinib arm versus those in the BAT comparator arm, providing an indirect QALY benefit for fedratinib, even in non-responders to fedratinib. This benefit applies even in the company's base-case in which suboptimal fedratinib is not available as part of subsequent BAT. Therefore in the company's base-case, non-responders to fedratinib have a QALY gain relative to non-responders to ruxolitinib, because one group is assumed to be eligible for subsequent treatment with non-JAK inhibitor forms of BAT and the other is not. The EAG has assessed the impact of this assumption by conducting a scenario analysis in which 100% of patients stopping treatment with fedratinib (responders and non-responders) go directly to supportive care and none receive subsequent BAT (see Section 4.4.2.3). It should be noted that in this analysis, there is zero usage of suboptimal fedratinib. However, the issue described here is not relevant in scenarios where usage of suboptimal fedratinib is consistent with usage of suboptimal ruxolitinib.

An alternative method to correcting this inconsistency would be to allow a proportion of patients who have received ruxolitinib as comparator BAT to transition to other forms of BAT after discontinuing ruxolitinib. This would ensure that the modelling of BAT is consistent in patients discontinuing both ruxolitinib and fedratinib. However, the EAG does not believe this can be implemented within the company's current model structure.

4.3.3.4 Inconsistent assumptions regarding utility gains in non-responders to fedratinib and BAT.

The EAG's main concern regarding the utility values applied in the model is the company's decision to assume no change in utility from baseline for non-responders to BAT, whilst applying a change in utility from baseline for non-responders to fedratinib. This is particularly problematic given that the regression analysis was conducted using data pooled across both arms of FREEDOM-2 and the regression did not include a covariate for treatment arm. The EAG prefers to apply the utility gain for non-responders estimated from the regression (0.052) to all patients who do not achieve a treatment, regardless of whether they received BAT or fedratinib (see Section 4.4.2.4).

4.3.3.5 Costing of ruxolitinib assumes high wastage due to dose changes

Whilst the EAG acknowledges that there may be some wastage of ruxolitinib arising from patients being required to change dosage mid-cycle to manage AEs, it considers that this is likely to be overestimated in the company's model. This is because the company's approach to estimating the dosing of ruxolitinib results in an average daily dose of [redacted] mg per patient, which is much higher than the mean dose per patient reported in the CS of 24.1 mg,[2] (this corresponds to a mean initial dose of 24.1 mg reported in CSR Table 4.3.1.1.2.2).[19] This discrepancy is due to the company assuming that every time a new patient dose is recorded mid-cycle, the remainder of the pack is discarded and a new pack of four weeks' worth of treatment is dispensed. This combined with the frequent requirements for dose adjustments within the trial population results in an average of [redacted] to [redacted] packs being prescribed per patient per cycle across the first 6 six cycles, when a single pack would usually provide one cycle of treatment. The EAG considers it unlikely that this level of wastage would occur in clinical practice. It notes that the dosing of ruxolitinib is dependent on platelet count and that haematology tests were required in the study protocol on day 1 of each cycle, with additional testing of days 15 of cycles 1 to 3, whereas equivalent tests are only assumed approximately every 3 weeks in the model. In addition, the EAG considers that the NHS would not routinely dispense treatment for a four-week period if dosing was dependent on a test being carried out every 2 weeks. The EAG therefore prefers to use the average initial dose distribution across the first 6 cycles (equivalent to a mean daily dose of 23.8 mg) with an assumption of 5% wastage for dose adjustments (see Section 4.4.2.5). Whilst this proportion of wastage is somewhat arbitrary, it was one of the scenarios considered by the committee in TA756, with the other being zero wastage.[9]

4.3.3.6 Uncertainty regarding the duration of suboptimal ruxolitinib within BAT

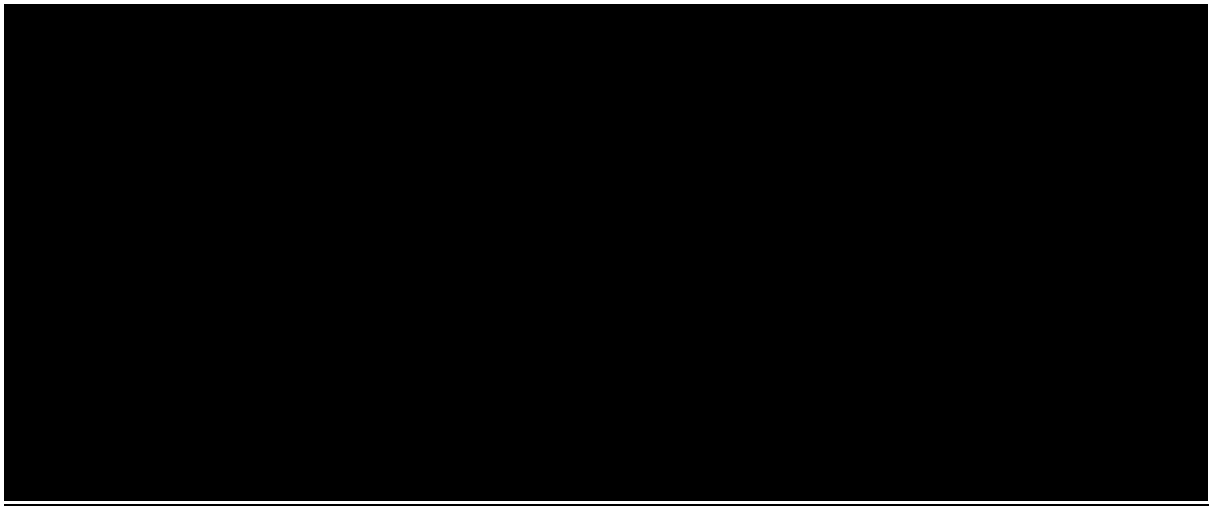
The EAG notes that the TTD curve for BAT includes time spent on fedratinib because patients crossing over from BAT to fedratinib were not censored at crossover in the KM plot for TTD (clarification response, question A19) and crossover to fedratinib was not considered a discontinuation event (clarification response, question B18b).[17] The EAG notes that crossover from BAT to fedratinib could occur either prior to month 6 if disease progression was established, or within 28 days of the end of cycle 6, with the latter being possible regardless of whether the patients responded to BAT. Crossover in the vast majority of patients in FREEDOM-2 occurred after month 6 (CS page 63; only 3 of the 46 crossover patients crossed before month 6 over due to disease progression)[2] and therefore crossover was not necessarily driven by disease progression or lack of response to BAT, but by a patient preference to receive fedratinib instead of BAT. The EAG considers that it is unclear whether the duration of treatment with BAT would have been similar if patients had not had the option to cross over to fedratinib. It is possible that fedratinib in the trial simply replaced the suboptimal ruxolitinib that would otherwise have been continued, meaning that a similar expected total duration of JAK inhibitor treatment would be expected, whether or not fedratinib was available. However, it is also possible that

the duration of treatment on BAT was longer in the trial than would be expected in clinical practice, because patients would not have persisted as long on suboptimal ruxolitinib. In addition, it is unclear whether equivalent OS outcomes would be expected if patient received a shorter duration of BAT in clinical practice. To explore these uncertainties, the EAG has conducted a scenario analysis in which it applied the TTD and OS curves fitted to the BAT cohort excluding those who crossed over to fedratinib. This is equivalent to company scenario 7 in Table 35. The EAG would have preferred to have applied curves fitted to KM data in which patients were censored at crossover rather than being excluded entirely from the KM data. However, the EAG does not believe that these are available within either the CS or the model, as the company stated that patients were not censored at crossover (company's response to clarification questions A19)[17] and the curves applied in company scenario 7 are described as "*no crossover for BAT,"* in CS, Table 83.[2] The EAG notes that it had some concerns regarding the methods used to select curves in the various company scenario analyses presented for OS and TTD extrapolation, which are described further in Section 4.3.3.14. However, despite these minor concerns, it considered that a scenario analysis using these TTD and OS curves fitted to the subgroup of patients without crossover provide a plausible alternative estimate of TTD and OS; although it acknowledges that these estimates are uncertain because of the small numbers of patients who did not crossover and the fact that these patients may be a selected group. Therefore, these estimates are only explored in EAG scenario analyses (see Section 4.4.2.7).

4.3.3.7 Estimates of OS and TTD from FREEDOM-2 may overestimate the time on treatment and OS expected in clinical practice

The EAG notes that median TTD and OS on fedratinib are both longer in FREEDOM-2 than in SACT (see Sections 3.3.6 and 3.3.8). Although the company provides some potential reasons for these differences, many of these relate to the characteristics of the population (e.g., a median age of 72 in SACT vs 70 years in FREEDOM-2, 76% males in SACT versus 56% in FREEDOM-2, uncertainty in the comparability of PS scores). The EAG would expect that the population treated in the future with fedratinib would be more likely to reflect the population treated in SACT than the population enrolled in FREEDOM-2. This is because the company states that its proposed positioning for fedratinib is consistent with its previous use within the CDF and patients included in the SACT dataset will have received fedratinib through the CDF. It is possible therefore, that the model overestimates both time on treatment and OS in the population likely to receive fedratinib in current practice. To explore this uncertainty the EAG has presented an exploratory scenario analysis using the SACT data to extrapolate TTD and OS in both the fedratinib and BAT arms. The methods in this scenario analysis are consistent with the company's scenario analysis presented in the company's clarification response (question B8),[17] but these data have been applied to the EAG's preferred base-case (see Section 4.4.2.8). The OS and TTD for this scenario are presented in
Figure 19.

Figure 19: OS and TTD applied in both treatment arms when using SACT data (the curves applied in the base-case using data from FREEDOM-2 are also plotted for comparison)



4.3.3.8 Some drug treatments received within BAT in the comparator arm of FREEDOM-2 are excluded from the model

The company's original model did not include the full set of treatments received within the BAT comparator arm of FREEDOM-2. Whilst functionality to include these treatments was included in the post-clarification model, this option was not selected for the company's updated post-clarification base-case. [49]The most notable discrepancy between the BAT composition applied in the company's base-case and composition of BAT in FREEDOM-2 was the absence of hydroxyurea, which was the third most commonly prescribed treatment within BAT (after ruxolitinib and RBC transfusions). In addition, whilst the company's base-case included 1.5% of patients receiving what it termed "hydroxycarbamide (hydroxyurea)," implying that hydroxycarbamide and hydroxyurea are different names for the same treatment, the inclusion of hydroxyurea, in 17.9% of patients receiving BAT within the company's scenario analysis, used different unit costs and dosing assumptions from those assumed for hydroxycarbamide. It is the EAG's understanding that these two drugs are equivalent, but only hydroxycarbamide is currently available as hydroxyurea is no longer listed in the BNF. The EAG therefore prefers to incorporate hydroxyurea in the model by increasing the proportion of patients receiving hydroxycarbamide (see Section 4.4.2.1). The EAG also prefers to include all drug treatments received within BAT in its preferred base-case (see Section 4.4.2.6), as the company has not provided a valid reason for excluding any of the treatments received in FREEDOM-2 from the BAT comparator (other drugs excluded were mercaptopurine, and methylprednisolone; each received by 1.5% of patients in the BAT arm). However, the EAG has not included RBC transfusions within BAT for the reasons discussed in Section 4.3.3.10.

4.3.3.9 Model uses MF-8D data from FREEDOM-2 and does not provide a reference case scenario using EQ-5D outcomes

The use of utility values obtained from the MF-8D has been previously accepted by NICE in the TA386 and TA756, although the EAG notes that in both cases, EQ-5D data were not available directly from the trial.[7, 9] The CS states, "*There are some concerns regarding the ability of the generic EQ-5D to detect clinically meaningful changes in the HRQOL of people with myelofibrosis. This includes the exclusion of relevant symptoms such as nausea and vomiting*,"[2] citing a paper by Mukuria *et al.*[51] However, the EAG considers that the company has misrepresented the findings of this paper. Mukuria *et al.* derived the MF-8D by combining items from the cancer specific EROTC QLQ-C30 tool with items from the myelofibrosis specific MFSAF tool.[51] They identified ceiling effects suggesting that nausea and vomiting are not relevant for patients with myelofibrosis and therefore excluded these items from the MF-8D. They conclude that the inclusion of disease-specific items and the exclusion of items such as nausea and vomiting that are not relevant means that the MFSAF is therefore better suited to generating utility values than methods that rely solely on the EORTC QLQ-C30, such as mapping from this measure to the EQ-5D or using the preference-based European Organisation for Research and Treatment of Cancer - 8 Dimension (EORTC-8D) which provides utility value from the EORTC QLQ-C30.[51] Mukuria *et al.* also recommend further research to compare MF-8D utility values with those generated by the EQ-5D.[51] Therefore the EAG does not consider that the company has provided a strong argument for not using the EQ-5D data directly measured in the trial given that these are available. The MF-8D shares some common methodology with the EQ-5D, such as using time trade-off (TTO) valuations in a UK general population sample to derive utilities for the health states provided by the descriptive system.[51] Given that this provides some degree of consistency with the NICE Reference Case,[50] and the fact that the MF-8D has been used in previous NICE appraisals of treatment for myelofibrosis, the EAG accepts that using MF-8D may be reasonable in this case. However, it would argue that the company should have also presented a Reference Case analysis using the EQ-5D data from the trial given that these were available.

4.3.3.10 Modelling of RBC transfusions

In the company's original model, RBC transfusions were only accounted for within resource use for routine management of myelofibrosis according to whether patients are receiving JAK inhibitors (either fedratinib or ruxolitinib), BAT other than ruxolitinib, or supportive care. Haematological AEs such as anaemia requiring RBC transfusions (or thrombocytopenia requiring platelet transfusions) were excluded from the model on the basis that these are captured within routine management for myelofibrosis. In addition, the company's original model did not account for RBC transfusions received as part of BAT. In response to clarification, the company added the option to include costs for patients receiving RBC transfusions as part of BAT within a scenario analysis.[17] The EAG disagrees with this

approach as RBC transfusions were allowed in both the BAT and fedratinib treatment arms and RBC transfusions received in patients randomised to fedratinib are not accounted for in the model.

The EAG notes that it is unclear whether the overall RBC transfusion burden was lower for fedratinib vs. BAT in FREEDOM-2 as fedratinib patients who were not transfusion-dependent at baseline had a lower risk of becoming transfusion-dependent (24% for fedratinib vs. 34% for BAT,

Table 14), whereas those who were transfusions-dependent at baseline had a lower probability of becoming transfusion-independent (3% for fedratinib vs. 18%1 for BAT,

Table 14). Also the mean number of units transfused per patient per 28 days was higher in the fedratinib arm (1.935 vs 1.408 units per patient per 28 days,

Table 14). In addition, anaemia response was reported in only 20% of participants in the fedratinib arm and 23% in the BAT arm (see

Table 14).

RBC transfusions are also included in the model as part of routine resource use, which differs according to the class of treatment received, with JAK inhibitors having a higher risk of RBC transfusion at the start of treatment and a lower risk in the long-term (CS, Table 67).[2] Patients receiving ruxolitinib as part of BAT are at the same risk of RBC transfusion as those receiving fedratinib and therefore are also at increased risk of RBC transfusion initially compared to those receiving other forms of BAT.

Based on the resource use assumed in the model (CS, Tables 66 and 67),[2] the EAG calculates from the model that the average number of RBC units transfused in those on treatment with fedratinib will be 29.33 units over 144 weeks, whereas the average number of units for those on treatment with BAT will be 28.89 units over 144 weeks. This is based on 77.6% of the BAT arm receiving ruxolitinib and having the same transfusion rate as fedratinib patients and the remainder of the BAT arm having a lower rate of 27.36 units over 144 weeks (0.190 units per week for BAT not including ruxolitinib). Therefore, the model predicts 2% higher RBC transfusion units in the fedratinib arm than in the BAT arm over the first 144 weeks of treatment (assuming patients persist for the full 144 weeks). However, the EAG considers this feature of the model to be inconsistent with the data on transfusions per patient per 28 days reported in FREEDOM-2, which were 37% higher (see

Table 14) in the fedratinib arm than the BAT arm (excludes BAT patients after crossover to fedratinib).

RBC transfusions in response to haematological AEs such as anaemia are not included in the model. It would be difficult to use haematological AEs to account for anaemia requiring transfusion, as the trial protocol states that hospitalisation for "*the administration of blood or platelet transfusion as routine treatment of studied indication*," are not to be considered serious AEs, with only hospitalisations related to complications of transfusions being counted as serious AEs.

On the basis that there is no evidence from FREEDOM-2 that fedratinib lowers the transfusion burden relative to BAT (where BAT includes suboptimal ruxolitinib in a high proportion of patients), the EAG has assumed an equal rate of RBC transfusions for JAK inhibitors and BAT, thereby rendering no difference in RBC transfusions between the fedratinib and BAT comparator arms (see Section 4.4.2.10). Due to the way the company's model calculates RBC usage for JAK inhibitors relative to non-JAK inhibitor treatments and applies the same RBC transfusion rate for fedratinib and ruxolitinib, the EAG was unable to conduct a more pessimistic scenario including an increased risk of RBC transfusion for fedratinib vs BAT.

4.3.3.11 Inconsistent approach to modelling sex-specific utilities

The company has provided limited details on the regression model fitted to the utility data from FREEDOM-2. The company states that mixed effects regression modelling was preferred over average utility values for the relevant subgroups (e.g., raw mean utility by responder status), as it accounts for multiple observations from the same patient and can simultaneously account for multiple covariates without compromising sample size, including differences in baseline utility (clarification response, question B23).[17] The EAG notes that there is quite a marked difference in baseline utility by sex (0.579 for females and 0.711 for males, CS Table 54)[2] and whilst the model is set up to allow separate utility values according to patient sex, the company has chosen not to account for differences in utility by sex, except when applying the multipliers to adjust for age-related decrements in the general population, which seems inconsistent.

The company's model does provide the option to use sex-specific utility values, but the EAG has identified an error in the implementation of this scenario analysis within the model, as it calculates separate utility changes from baseline for male and female responders and non-responders but then applies the female changes from baseline to the male baseline utility. The EAG has corrected this error within its exploratory analysis (see Table 27 and Section 4.3.3.1) and has included a scenario analysis using sex-specific utility values (Section 4.4.2.9). The EAG notes that when using the sex-specific utilities approach, the absolute utility values and the change in utility from baseline for responders and non-responders differs by sex, but the difference between responders and non-responders is consistent

across males and females (0.115) and is consistent with the value from the regression using pooled data form males and females. As the modelled QALY gain for fedratinib versus BAT is mainly driven by differences in the response rate between fedratinib and BAT, it is the differences in utility between responders and non-responders that is most important. The EAG therefore considers that using gender-specific utility values is a reasonable alternative approach, which captures both the treatment effect of fedratinib, and the differences in baseline utilities by sex.

4.3.3.12 Utility gains for responders applied from 4 weeks when response is determined at 6 months

Utility change according to response is applied in the model at 4 weeks despite response being assessed at 6 months and patients maintain their disease-specific utility value over time until they move to the supportive care state. The EAG notes that patients are categorised in the regression according to their response status at 6 months, and not their response or disease-progression status at the time of the HRQoL measurement. This means that patient's MF-8D scores measured on day 1 of cycles 1 to 6 will be included in the regression and categorised according to whether they achieved a response at the end of cycle 6, regardless of whether they would have met the criteria for response at the time HRQoL was measured. The impact of this is unknown, as it would depend on how quickly HRQoL improved in those who go on to achieve a response at the end of cycle 6. However, the EAG does consider that the company's approach risks over-estimating the treatment benefit because it ascribes the utility gain associated with response from 4 weeks onwards. The CS reports that the median time to spleen response by palpation (defined as a ≥ 50% reduction in spleen size by palpation for participants with a palpable spleen at least 5 cm below the LCM at baseline) was 20.3 weeks (95% CI, 12.6-45.9) in the fedratinib arm,[2] although this was not estimated specifically in the subgroup who achieved a response within 6 months. A KM plot of time to spleen response by palpation suggests that response is achieved fairly rapidly with around half of the response achieved by 6 months occurring in the first [redacted] weeks (CSR Figure 14.2.5.7).[19] The EAG would have liked to have conducted a scenario analysis to explore the impact of assuming no change in utility according to response until 8 weeks. However, this adaption of the company's model was not considered feasible in the time available as the 4-week duration is hardwired into the VBA code in multiple places.

4.3.3.13 Definition of response using either spleen volume or symptoms

The company's model applies a combined definition of response in which any patient achieving either a spleen volume response (SVR ≥ 35%) or a symptom response (TSS reduction ≥ 50%) is considered a responder in the model and is assumed to have equivalent gains in HRQoL. There is internal consistency in this approach in that the definition of response used in the utility regression was consistent with the definition of response applied in the model. However, the EAG does not consider that the company's rationale for using this combined definition is reasonable given that it relies on the clinical advice that these two measures track each other whereas in FREEDOM-2 there was low agreement between

classification of responders between the two definitions. In addition the EAG notes that based on the company's regression using each individual definition, the utility gain associated with a symptom response is greater than that associated with a spleen volume response suggesting that there may be some heterogeneity in benefits according to the type of response achieved. The EAG has therefore conducted two scenario analyses in which each individual definition of response (spleen only and symptoms only) has been used to determine response rates and utility gain for responders (see Section 4.4.2.11).

4.3.3.14 Uncertainty in the scenario analyses presented for OS and TTD extrapolation

The company has conducted a number of different scenario analyses described as "*adjusting for a treatment-switching effect without using formal crossover-adjustment methods*". These analyses, described in CS Table 47,[2] model the survival data separately according to treatment group and/or responder status, for the three different definitions of responder status. Results are provided for the base-case definition of responder status only (SVR or TSS) but the results for the other 2 definitions are described by the company as "*consistent with those presented*" and can be implemented in the model. The model fitting results provided in CS B.3.3.6 and Appendix M for these additional scenarios have been summarised by the EAG in Table 37

Table 37 (OS) and

Table 38

Table 38 (TTD), which also indicates which of these have been considered as scenarios in the company's scenario analysis (see Table 35).[2]

However, for some of the analyses described in the company's modelled scenarios analyses (see Table 35), it was not clear to the EAG that these had been described in the model selection process presented in the main submission or appendices. The EAG notes that it was unable to replicate the reported ICER ([redacted]) for scenario 7 which reported using "no crossover" data for BAT, but it did obtain a similar ICER [redacted] using the settings reported by the company in Table 9 of the updated results post-clarification document (see Table 35).[49] Figure 20Figure 12 summarises OS and TTD applied across both arms in scenario 7. The OS data for BAT patients who did not cross over to fedratinib appears to have been analysed for non-responders as the data applied in the model appear to match CS Appendix M, Figure 19. The TTD curve applied in scenario 7 appears to match data in CS, Figure 41.[2] The same curves are applied for both responders and non-responders in this scenario and the base-case settings are maintained for the fedratinib arm. It is unclear to the EAG why the Weibull model has been selected for OS in this scenario when the log-logistic and log-normal are identified as being the two most plausible extrapolations in the no crossover BAT population (CS, Appendix M, page 163). The EAG notes that this scenario had a large impact on the cost-effectiveness results in the company's scenario analysis as it allowed for large differences in both OS and TTD between the fedratinib and BAT arms (see Figure 20), whereas the company's base-case assumed OS and TTD were equivalent in both treatment groups. Given that the crossover design of FREEDOM-2 limits the ability to determine whether OS and TTD differ between fedratinib and BAT, the EAG has explored applying these curves to its preferred base-case scenario (see Section 4.4.2.7), in order to demonstrate the uncertainty inherent in the cost-effectiveness analysis due to the lack of long-term comparative data (see Section 4.3.3.6).

In scenarios 9 and 10, where OS and TTD are split by both treatment and response status, the OS data from the BAT patients who did not cross over are assumed to provide an estimate of OS in patients who responded to BAT treatment. This was because there were no deaths reported in the small number of patients who were responders in the BAT arm. The EAG considers this to be an odd choice given that crossover to fedratinib at 6 months was not dependent on response status and the analysis of OS outcomes for BAT patients without crossover appears to only include non-responders. The EAG notes that the log-normal extrapolation has been used in these scenarios for the BAT arm population excluding crossovers, which is inconsistent with the choice of parametric curve in company scenario 7.

Figure 20: Time-to-event outcomes applied in company scenario 7 which explores the impact of using data from the BAT 'no crossover' cohort to model OS and TTD in the BAT arm

Overall, the EAG considers that the company's base-case is reasonable. But given the reasonably small sample size and the failure of formal methods to account for treatment switching, attempting to resolve this by creating even smaller groups based on treatment arm and response status is not appropriate. This is highlighted by lack of OS events in the BAT responders group, which leads to inconsistent modelling assumptions for different groups; such as scenarios 11 and 12 which use data pooled over treatment arm to model BAT responders, but separate subgroups otherwise. The company failed to provide non-parametric estimates of the hazard in response to clarification question B14, stating that "*given the small sample size, it was judged that hazard estimates would be too noisy to be informative*".[17] The company's assessment of the PH assumption for groups based on responder status concluded that the assumption did not hold for the observed data, but despite this it provides scenario analyses based on this assumption. The CS states that "*the option to pool fedratinib and BAT together has been chosen to ensure that the OS survival function for BAT did not cross the OS survival function for fedratinib, which was deemed implausible by clinical experts consulted during an advisory board.*"[2] However, when fitting parametric models separately to each treatment group (Appendix M.1.1.3) it uses the "*crossing of survival curves*" to justify separate models for each treatment group, which is necessary to allow the model estimates to cross. The EAG is concerned that the company has explored multiple approaches to extrapolating OS and TTD without applying a consistent and logical rationale throughout the whole process. Also, the choice to model OS separately by treatment arm and response status does not align with the choice of regression model for utilities (which accounted for responder status but not treatment; see Section 4.2.5.4). However, as the company's base-case model uses data pooled across the fedratinib

and BAT treatment groups, and the EAG considers that this is reasonable given the data (see Section 4.2.5.1), it considers the limitations in the company's approach to selecting curves for these scenarios analyses to be a minor issue.

Table 37: Summary of parametric model selection scenario analyses for OS

Analysis	Treatment	Responder	Rationale and notes	Model selection (numbers indicate model scenario in Table 35)
Base-case	Pooled Fedratinib/ BAT	NA	Assumes that there was no OS difference by treatment arm. Avoids fedratinib curve predicting OS lower than BAT which was deemed implausible.	Weibull (1 base-case, 3, 5, 6) Gompertz (2)
Pooled by responder status	Fedratinib	NA	Log-normal and exponential best fitting by AIC/BIC	Weibull for both (4) Weibull for BAT only (8) Log-normal for fedratinib only (8)
	BAT	NA	Weibull and gamma best fitting model by AIC/BIC. Same model chosen for both arms. Based on clinicians' estimates and assumption that fedratinib does not have worse OS than BAT.	
	Fedratinib/ BAT with covariate for treatment effect	NA	Not conducted. CS considered inappropriate due to crossing of survival curves	
	BAT excluding crossover (n=21)	NA	Tests the impact of the assumption of no crossover for BAT Weibull fitted to BAT excluding crossovers (7)	
Separate by responder status	Fedratinib	Responder	Log normal best fit by AIC/BIC Concludes that potentially none appropriate due to curves crossing and or implausibly high long term extrapolations.	Log-normal (9)
		Non-responder		Log-normal (9)
		Responder and non-responder with covariate	Preferred by CS as ensures that curves do not cross. But EAG notes this is not consistent with response to clarification question B14 that shows that the PH assumption is violated.[17]	Weibull (10, 11) Exponential (12)

			Weibull and gamma have poor fit based on AIC/BIC but other models have implausible extrapolations.	
	BAT	Responder	No deaths, not conducted	Uses data/results for pooled fedratinib/BAT Weibull (11) exponential (12)
		Non-responder	Weibull best fit by AIC/BIC but all similar Log-logistic and log normal only plausible options	Log-logistic (11) Log-normal (12) Weibull (9)
	BAT excluding crossover (n=21)	Responder	Generalised gamma best fit by AIC/BIC but all similar Only log-normal met assumption of lower survival than BAT non-responders including crossover	Log-normal (9,10)

Abbreviations: BAT – best available therapy; AIC - Akaike information criterion; BIC - Bayesian information criterion; PH – proportional hazards; NA – not applicable; OS – overall survival

Table 38: Summary of parametric model selection scenario analyses for TTD

Analysis	Treatment	Responder	Rationale and notes	Model selection (model scenario)
Base-case	Pooled Fedratinib/ BAT	NA	Assumes that there was no TTD difference by treatment arm. Avoids fedratinib curve predicting TTD lower than BAT	Log-logistic (1 base-case, 2, 6) Generalised gamma (3)
Pooled by responder status	Fedratinib	NA	TTD generally higher for BAT with curves crossing towards the end of follow up	Exponential for both (4, 5) Log-normal for fedratinib only (8) Log-logistic for BAT only (8)
	BAT	NA		
	BAT excluding crossover (n=21)	NA	CS, Figure 41, Table 51.[2]	Log-logistic (7)
Separate by responder status	Fedratinib	Responder	Unlike BAT arm, clear separation of curves with lower rates of discontinuation for responders Selects same model type for responders/non-responders. Log-normal best overall fit across responders/non-responders	Generalised gamma (9) Log-normal (10)
		Non-responder		Log-logistic (9) Log-normal (10)
	BAT	Responder	Generalised gamma best fitting model by AIC/BIC Concludes different models appropriate for responders and non-responders.	Generalised gamma (9, 10)
		Non-responder	Exponential best fitting model by AIC/BIC	Exponential (9, 10)

Abbreviations: BAT – best available therapy; AIC - Akaike information criterion; BIC - Bayesian information criterion; PH – proportional hazards; NA – not applicable; TTD – time to treatment discontinuation

4.4 Exploratory analyses undertaken by the EAG

4.4.1 Overview of the EAG's exploratory analyses

The methods for the EAG's exploratory analyses are provided in Section 4.4.2 with results provided in Section 4.4.3. The EAG has indicated in each case which changes are included in its base-case and which are included only in its scenario analyses.

4.4.2 EAG's exploratory analyses – methods

4.4.2.1 Correction of errors in the company's model and updated drug acquisition costs

The EAG corrected the company's implementation errors mentioned in Section 4.3.3.1 as follows:

- Inclusion of age-related utility multipliers for males where separate multipliers were calculated for males and used instead of the female multipliers.
- Changes from baseline for males are applied to male utility values (correction only affects the scenario analysis using sex-specific utility values described in Section 4.4.2.9).
- The AML rate for BAT was set equal to that for fedratinib by adjusting time of exposure to reflect COMFORT-II.
- Costs related to supportive care are discounted starting from the time patients discontinue fedratinib and/or BAT.
- Added proportion on hydroxyurea to those on hydroxycarbamide (correction only affects scenarios where hydroxyurea is included, which includes EAG's preferred base-case; see Section 4.4.2.6).
- Corrected PSA implementation by using the same set of random number for sampling time-to-event parameters regardless of treatment arm or response status.

Updated drug acquisition prices sourced from eMIT to reflect those from the NICE pricing tracker form (see

- Table 39).

All of these changes were included in the EAG's preferred base-case and the model including these changes was used as the starting point for the analyses described below.

Table 39: Drug acquisition prices and sources for EAG analyses and company's analyses

Treatment	Pack size	Unit size	Company's base-case		EAG's exploratory analyses in Section 4.4		Confidential appendix
			Pack cost	Source	Pack cost	Source	Source
Fedratinib	120 tablets	100 mg	[redacted]	Company	[redacted]	Company	Company
Ruxolitinib 5 mg	56 tablets	5 mg	£1,428	MIMS	£1,428	MIMS	NICE
Ruxolitinib 10 mg	56 tablets	10 mg	£2,856	MIMS	£2,856	MIMS	NICE
Ruxolitinib 15 mg	56 tablets	15 mg	£2,856	MIMS	£2,856	MIMS	NICE
Ruxolitinib 20 mg	56 tablets	20 mg	£2,856	MIMS	£2,856	MIMS	NICE
Danazol	30 capsules	200 mg	£97.64	eMIT	£100.37	eMIT [a]	eMIT [a]
Hydroxycarbamide	100 capsules	500 mg	£10.00	MIMS	£9.97	eMIT [a]	eMIT [a]
Interferon alfa	3 prefilled syringes	3 million IU/0.5 ml	£14.20	MIMS	£14.20	MIMS	MIMS
Prednisolone	28 tablets	5 mg	£0.30	eMIT	£0.41	eMIT [a]	eMIT [a]
Prednisone	28 tablets	5 mg	£0.94	BNF	£0.94	BNF	BNF
Thalidomide	28 capsules	50 mg	£298.48	MIMS	£283.60	eMIT [a]	eMIT [a]
RBC transfusion	1	1	£709.61	NHS Reference costs	£709.61	NHS Reference costs	NHS Reference costs
Hydroxyurea	25 capsules	50 mg	£14.37	MIMS	£14.37	MIMS	MIMS
Mercaptopurine	25 tablets	50 mg	£8.45	MIMS	£8.45	MIMS	MIMS
Methylprednisolone	20 tablets	100 mg	£48.32	MIMS	£48.32	MIMS	MIMS

[a] *eMIT version accessed was last updated on 5th April 2024*

4.4.2.2 Composition of BAT received after fedratinib.

The EAG preferred to assume that 77.6% of people on fedratinib would receive suboptimal fedratinib after reaching their discontinuation time based on TTD from FREEDOM-2 (see Section 4.3.3.2). As the company's model already included an option to include suboptimal fedratinib, this was implemented in the model by setting the proportion receiving suboptimal fedratinib for both responders and non-responders to 77.6% and by setting the proportion receiving BAT after discontinuing fedratinib to 100% (i.e., 0% transitioning directly to supportive care). This assumption was incorporated in the EAG's preferred base-case.

4.4.2.3 Transition probabilities to supportive care after fedratinib

The EAG conducted a scenario analysis where all patients transition to supportive care after fedratinib discontinuation (see Section 4.3.3.3). As the company's model already included an option to set the proportion receiving BAT after fedratinib, the EAG simply set this value to 0% for both responders and non-responders. This assumption was not included in the EAG's preferred base-case, but it was applied as a scenario to the company's base-case to demonstrate the impact of the company's assumption that

patients stopping ruxolitinib cannot receive other BAT treatments, whilst patients stopping fedratinib can.

4.4.2.4 Utility gain for non-responders on BAT

The EAG applied the utility gain for non-responders estimated from the regression (0.052) to non-responders on BAT, in line with the value applied for fedratinib non-responders (see Section 4.3.3.4). This was implemented using the existing option provided in the company's model. This assumption was incorporated in the EAG's preferred base-case.

4.4.2.5 Ruxolitinib acquisition costs

For ruxolitinib cost calculations, the EAG used the average initial dose distribution across the first 6 cycles in its base-case (equivalent to a mean daily dose of 23.8 mg) with an assumption of 5% wastage for dose adjustments (see Section 4.3.3.5). This was implemented using by changing the dose distribution implemented in the model and using the existing option provided in the company's model to account for wastage. This assumption was incorporated in the EAG's preferred base-case.

4.4.2.6 Composition of BAT in the comparator arm

The EAG used the full set of drug treatments received within the BAT comparator arm of FREEDOM-2 (see section 4.3.3.8). The only exclusion is RBC transfusions, as discussed in Section 4.3.3.8 and 4.3.3.10. This was implemented using the company's existing option to include the additional treatments, with an additional switch added by the EAG to set the proportion receiving RBC transfusions to zero. This assumption was incorporated in the EAG's preferred base-case.

4.4.2.7 OS and TTD curves for BAT excluding patients who crossed over to fedratinib

The EAG conducted as scenario analysis exploring the impact of using data in the BAT arm only from patients who did not crossover to fedratinib (company scenario 7; see Sections 4.3.3.6 and 4.3.3.14). The curves applied are shown in Figure 20. This assumption was not included in the EAG's preferred base-case, but is presented as a scenario using the EAG's preferred base-case as the starting model.

4.4.2.8 OS and TTD curves from SACT

The EAG has also presented an exploratory scenario analysis using the SACT data to extrapolate TTD and OS in both the fedratinib and BAT arms (see Section 4.3.3.7). The methods in this scenario analysis are consistent with the company's scenario analysis presented in the company's clarification response (question B8).[17] This assumption was not included in the EAG's preferred base-case, but is presented as a scenario using the EAG's preferred base-case as the starting model.

4.4.2.9 Using sex-specific utility values

The EAG conducted a scenario analysis where the sex-specific utility values from the regression were used in place of the pooled analysis (see Section 4.3.3.11). This includes the correction to sex-specific utility values described in Section 4.4.2.1. This assumption was not included in the EAG's preferred base-case, but is presented as a scenario using the EAG's preferred base-case as the starting model.

4.4.2.10 RBC transfusions assumed the same between fedratinib and BAT

The company's approach results in lower RBC transfusions for fedratinib, but the EAG does not consider that this is clearly supported by the evidence (see Section 4.3.3.10). The EAG therefore prefers to adjust the resource use for JAK inhibitors, so the same rate of RBC transfusions is applied for both JAK inhibitors and BAT, thereby setting the RBC transfusion to be equivalent between patients starting treatment with fedratinib and patients starting treatment with BAT (including suboptimal ruxolitinib). This assumption was incorporated in the EAG's preferred base-case.

4.4.2.11 Response rates according to definition

The EAG conducted two scenario analyses where response rates from FREEDOM-II were changed to use either spleen response (SVR ≥ 35%) or symptom response (TSS reduction ≥ 50%), based on the response rates shown in

Table 12 (see Section 4.3.3.13). This was implemented using options already available with the company model. This assumption was not included in the EAG's preferred base-case, but is presented as a scenario using the EAG's preferred base-case as the starting model.

4.4.3 Results of the EAG's exploratory analyses

4.4.3.1 Impact of individual changes constructing the EAG's base-case

The EAG's exploratory analyses showing the impact of making individual changes to the company's base-case model are provided in Table 40. The exploratory analysis that has the most significant impact on the INMB for fedratinib is implementing the EAG's preferred costing method for ruxolitinib, which decreases the INMB (when valuing a QALY at £20,000) from £[redacted] to £[redacted], mainly due to the decrease in cost savings associated with fedratinib from [redacted] to [redacted].

The second most significant change impacting the INMB is assuming a proportion to receive suboptimal fedratinib similar to those receiving suboptimal ruxolitinib in the BAT comparator arm. This reduces the cost savings to [redacted] which decreases the INMB from £[redacted] to £[redacted]. The other changes did not have a substantial impact on either the cost savings or the INMB.

Table 40: EAG's exploratory analyses (impact of individual changes constructing the EAG's base-case)

Option	QALYs	Costs	Incremental		INMB (at £20,000 threshold)	ICER [a]
			QALYs	Costs		
Company base-case – post-clarification (Deterministic)						
BAT	[redacted]	[redacted]	-	-	-	Dominant
Fedratinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 1: Correcting programming and implementation errors in the company's economic model and updated drug acquisition costs						
BAT	[redacted]	[redacted]	-	-	-	Dominant
Fedratinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 2: Proportion receiving suboptimal fedratinib after fedratinib is equal to proportion receiving suboptimal ruxolitinib in the BAT comparator arm						
BAT	[redacted]	[redacted]	-	-	-	Dominant
Fedratinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 3: Utility gain for non-responders to BAT equal to utility gain for non-responders to fedratinib						
BAT	[redacted]	[redacted]	-	-	-	Dominant
Fedratinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 4: Ruxolitinib costing based on average initial dose distribution across the first 6 cycles in FREEDOM-2 plus 5% wastage for dose adjustments						
BAT	[redacted]	[redacted]	-	-	-	Dominant
Fedratinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 5: BAT comparator arm includes all drug treatments received within FREEDOM-2 (with the exclusion of RBC transfusions)						
BAT	[redacted]	[redacted]	-	-	-	Dominant

Option	QALYs	Costs	Incremental		INMB (at £20,000 threshold)	ICER [a]
			QALYs	Costs		
Fedratinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 6: RBC transfusion rate assumed equal between fedratinib and BAT						
BAT	[redacted]	[redacted]	-	-	-	Dominant
Fedratinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 7: Assuming all patients on fedratinib transition to supportive care after discontinuation						
BAT	[redacted]	[redacted]	-	-	-	Dominant
Fedratinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BAT - best available therapy; EAG - external assessment group; ICER - incremental cost-effectiveness ratio; INMB - incremental net monetary benefit; QALYs- quality-adjusted life-years; RBC - red blood cells
[a] Dominant indicates that fedratinib has lower costs and higher QALY gains.

4.4.3.2 The EAG's estimate of the ICER

In the EAG's preferred base-case, which combined EAG's exploratory analyses 1 to 6, fedratinib no longer dominates BAT. Instead it has an ICER of £[redacted] per QALY, as shown in Table 41. This is mainly due to the impact of the EAG's preferred methods to calculate ruxolitinib costs in addition to allowing patients in the fedratinib arm to have suboptimal fedratinib after reaching their treatment discontinuation time estimated from FREEDOM-2. The probabilistic ICER for the EAG's preferred base-case was £[redacted] per QALY. Fedratinib had an ICER under £30,000 per QALY in [redacted]% of PSA runs.

The EAG has also conducted deterministic scenario analyses, shown in Table 41, using its preferred base-case scenario as the starting point. The ICER in these scenarios ranged from fedratinib being dominant when 100% of patients in the fedratinib arm were assumed to transition directly to supportive care (i.e. assuming no subsequent BAT), to an ICER of £[redacted] per QALY when SACT data are used as the source for modelling OS and TTD. The scenario analyses also suggest that the ICER is particularly sensitive to the assumption that the OS and TTD curves including patients who crossed over to fedratinib are predictive of TTD and OS for patients receiving BAT in clinical practice. Using data for only the patients on BAT who did not cross over to fedratinib increased both the incremental costs and QALYs associated with fedratinib. Other factors like using sex-specific utility values or modelling response rates according to either spleen response or symptom response alone do not have substantial impact on the ICER.

Table 41: EAG's base-case and scenario analyses

Option	QALYs	Costs	Incremental		INMB (at £20,000 threshold)	ICER
			QALYs	Costs		
EAG's base-case including changes 1-6 in Table 40 (Deterministic)						
BAT	[redacted]	[redacted]	-	-	-	[redacted]

Option	QALYs	Costs	Incremental QALYs	Incremental Costs	INMB (at £20,000 threshold)	ICER
Fedratinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
EAG's base-case including changes 1-6 in Table 40 (Probabilistic)						
BAT	[redacted]	[redacted]	-	-	-	[redacted]
Fedratinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
EAG scenario analysis 1: Assuming all patients on fedratinib transition to supportive care after discontinuation						
BAT	[redacted]	[redacted]	-	-	-	Dominant
Fedratinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario analysis 2: Using OS and TTD data in the BAT arm only from patients who did not crossover to fedratinib as with company's scenario 7						
BAT	[redacted]	[redacted]	-	-	-	[redacted]
Fedratinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
EAG scenario analysis 3: Using OS and TTD data from SACT as with company's scenario in response to clarification question B8						
BAT	[redacted]	[redacted]	-	-	-	[redacted]
Fedratinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
EAG scenario analysis 4: Using sex-specific utility values from the regression analysis in place of the analysis pooled across males and females						
BAT	[redacted]	[redacted]	-	-	-	[redacted]
Fedratinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
EAG scenario analysis 5: Using only spleen response to model response rates						
BAT	[redacted]	[redacted]	-	-	-	[redacted]
Fedratinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
EAG scenario analysis 6: Using only symptom response to model response rates						
BAT	[redacted]	[redacted]	-	-	-	[redacted]
Fedratinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: BAT - best available therapy; EAG - external assessment group; ICER - incremental cost-effectiveness ratio; INMB - incremental net monetary benefit; OS - overall survival; QALYs- quality-adjusted life-years; RBC - red blood cells; SACT - systemic anti-cancer therapy; TTD - time to treatment discontinuation

5 OTHER FACTORS

The company has not submitted any evidence to support the implementation of a severity modifier in this appraisal and did not provide the necessary calculations to estimate the absolute and proportional QALY losses. However, based on its own calculations (see Table 42), the EAG does not believe that the requirements for a severity modifier would be met in this appraisal. This is because the absolute QALY shortfall is less than 12, and the proportional QALY shortfall is under 0.85, in both the company and the EAG's preferred base-case scenarios, as shown in Table 42. A managed access scheme has not been proposed.

Table 42: Severity modifier calculations

Analysis	Lifetime expected QALYs for the general population[a]	Lifetime expected QALYs under current SoC[b]	Absolute QALY shortfall	Proportional QALY shortfall	QALY weight
Company - modelled comparator arm and modelled general population	9.51	[redacted]	[redacted]	[redacted]	1.0
EAG - modelled comparator arm for EAG base-case and modelled general population.	9.51	[redacted]	[redacted]	[redacted]	1.0

Abbreviations: EAG – External Assessment Group; QALY – Quality-adjusted life-years; SoC – standard of care

[a] Estimated using the Online QALY Shortfall Calculator by Schneider et al.,[52] using patient characteristics for target population from company's economic model

[b] Estimated from company's economic model; using either company base-case or EAG preferred base-case settings

6 OVERALL CONCLUSIONS

Clinical evidence: The CS presents data from the FREEDOM-2 RCT of fedratinib vs. BAT and the SACT dataset of fedratinib in the CDF population, both in myelofibrosis patients with prior ruxolitinib. No comparison against momelotinib is reported. In FREEDOM-2, at EOC6, spleen volume response rate (SVR ≥ 35%) was 36% for fedratinib vs. 6% for BAT (p<0.0001); symptom response rate (TSS reduction ≥ 50%) was 34% for fedratinib vs. 17% for BAT (p=0.0033); and spleen or symptom response rate (used in the company model) was 52% for fedratinib vs. 19% for BAT (p=not reported). Time-to-event outcomes were confounded by the fact that 69% of patients in the BAT arm crossed over to fedratinib by EOC6. Median durability of spleen volume response was 86 weeks for fedratinib and not estimable for BAT, and median durability of symptom response was 12 weeks for fedratinib and 10 weeks for BAT. Time to treatment discontinuation (used as a proxy for duration of response in the model) was [redacted] weeks for fedratinib and [redacted] weeks for BAT in FREEDOM-2, and 25 weeks for fedratinib in SACT. OS was not estimable (95% CI: 113 weeks to not estimable) for fedratinib and 125 weeks for BAT in FREEDOM-2, and 67 weeks for fedratinib in SACT. The EAG agrees with the company that none of the methods for crossover adjustment were appropriate; therefore it is difficult to draw conclusions about comparative OS for fedratinib versus BAT. The most common AEs in the fedratinib arm were diarrhoea (46%), anaemia (44%), nausea (40%), thrombocytopenia (36%), constipation (22%) and asthenia (20%), and in the BAT group (without crossover) were anaemia (36%), asthenia (24%), thrombocytopenia (18%) and nausea (15%).

Cost-effectiveness evidence:

The CS presents an economic analysis of fedratinib versus BAT in patients previously treated with ruxolitinib. The EAG notes that this is a subgroup of the population specified in the NICE scope, but it is consistent with the population who were eligible for fedratinib within the CDF under TA756.[9, 15] The composition of the BAT comparator was informed by the treatments received in the comparator arm of FREEDOM-2 and included a high proportion receiving suboptimal ruxolitinib (i.e., continued ruxolitinib treatment despite lack of response or loss of response to ruxolitinib previously). The company's economic evaluation assumed equivalent OS and TTD outcomes for the fedratinib and BAT arms of the model and used data pooled across both arms of the FREEDOM-2 study to extrapolate OS and TTD in both arms of the model. The model incorporates a higher response rate for fedratinib versus BAT based on the trial outcome of spleen or symptom response at month 6 in FREEDOM-2. In the company's base-case, fedratinib was found to dominate BAT, i.e., it was estimated to provide higher QALYs at a lower overall cost.

The lower overall cost for fedratinib in the company's base-case is mainly due to the company assuming a high degree of drug wastage in patients receiving ruxolitinib as BAT, which the EAG considers is

unlikely to reflect what happens in clinical practice. The company's approach used the total count of doses received to estimate the dose distribution. It assumed that a pack of treatment, sufficient for a whole cycle, is dispensed each cycle and each time the dose is changed mid-cycle, with the remainder of any packs being discarded. This led to an average dose, when including wastage, that was nearly double the average initial dose for ruxolitinib; resulting in much higher acquisition costs for BAT than fedratinib. The EAG prefers to use the initial dose distribution and account for wastage separately by assuming that 5% of medication dispensed is wasted. The EAG's exploratory analysis demonstrates that its alternative approach to calculate ruxolitinib costs has a substantial impact on the INMB (when valuing a QALY at £20,000), decreasing it to [redacted] (from [redacted]) when applied as a single change to the company's base-case.

The QALY gain for fedratinib versus BAT in the company's base-case is partially driven by the company's assumption that patients who do not respond to fedratinib have a utility gain from baseline, whereas those who do not respond to BAT cannot experience an equivalent utility gain. This is despite the fact that these utility gains were derived from a regression analysis which pooled data across treatment arms from FREEDOM-2 and did not include a covariate for treatment arm. The EAG therefore preferred to assume equivalent utility gains for non-responders in both arms of the model. Applying this single change to the company's base-case reduced the incremental QALYs from [redacted] to [redacted].

The QALY gain for fedratinib versus BAT in the company's base-case analysis is also partially driven by the company's assumption that patients stopping treatment with BAT, including those having suboptimal ruxolitinib, transition directly to supportive care, which is associated with lower utility values. In contrast, those stopping treatment with fedratinib are able to have other forms of BAT before transitioning to supportive care, thereby delaying the decline in utility associated with supportive care. The EAG's exploratory analyses demonstrated that 17% of the incremental QALY in the company's base-case were associated with this delay in supportive care.

The EAG also noted that there were different assumptions implied by the model structure whereby patients on BAT are allowed to receive suboptimal ruxolitinib, whereas patients on fedratinib cannot receive suboptimal fedratinib in the company's base-case. The EAG preferred to assume that the proportion receiving suboptimal fedratinib as subsequent BAT in the fedratinib arm would be similar to the proportion receiving suboptimal ruxolitinib in the BAT comparator arm, as this is in-line with the committee's preference in TA756.[9] This has a substantial impact on the INMB (when valuing a QALY at £20,000), decreasing it to [redacted] (from [redacted]) when applied as a single change to the company's base-case.

Overall, the EAG's preferred base-case ICER was £[redacted] per QALY for the deterministic analysis and £[redacted] per QALY for the probabilistic analysis. Therefore, fedratinib no longer dominates BAT in the EAG's preferred base-case, and the EAG's estimate of the ICER is above £30,000 per QALY.

However, the EAG considers that it base-case ICER is associated with considerable uncertainty, for several reasons. Firstly, it relies on using TTD estimates from the FREEDOM-2 study in which patients in the BAT arm were allowed to crossover to receive fedratinib and those patients were not censored or considered to have discontinued BAT at the point at which they switched treatment. The EAG considers that there is considerable uncertainty regarding whether the expected duration of treatment with BAT would be similar if patients did not have the option to switch to an alternative JAK inhibitor. Secondly, the EAG notes that median treatment duration was lower in the real-world data from the SACT database and OS outcomes were also more pessimistic. This means that the TTD and OS data from FREEDOM-2 may not be generalisable to the population likely to receive fedratinib in clinical practice, which the EAG expects to be closely aligned to those included in the SACT database. The EAG explored the impact of using alternative data to model OS and TTD, and showed a higher ICER when SACT data were used, and a lower ICER when data for patients on BAT who did not cross over to fedratinib in FREEDOM-2 were used to model the BAT arm. The EAG retained the company's approach using data pooled cross both arms to model OS and TTD in its base-case analysis. However the scenario analyses conducted by the EAG indicate that the TTD and OS estimates are an area of remaining uncertainty. Thirdly, the EAG considers that the ICERs are sensitive to assumptions regarding which treatments would be received next after fedratinib, as the scenario analysis in which all patients are assumed to transition directly to supportive care after fedratinib, rather than receiving any form of BAT, resulted in fedratinib dominating BAT.

Finally, the EAG notes that the CS does not provide a comparison of fedratinib against momelotinib, which was recommended in TA957 for the subgroup of patients with severe to moderate anaemia.[11] Although the comparison of fedratinib versus BAT which is presented in the CS could be interpreted as being a relevant comparison for the subgroup without moderate to severe anaemia. The EAG also notes that patients in both arms could potentially switch to momelotinib if they develop moderate to severe anaemia after starting treatment with either fedratinib or BAT. However, this possibility is not accounted for in the company's model. Therefore, the impact of momelotinib being available under TA957 is also unknown for the comparison of fedratinib versus BAT in patients who do not have moderate to severe anaemia when starting treatment.

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Single Technology Appraisal

Fedratinib for treating disease-related splenomegaly or symptoms in myelofibrosis (Review of TA756) [ID5115]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 3 June 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Inaccurate wording related to Modelling of costs

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Section 1.2 (page 12), the EAG report states: "Overall, in the company's base-case analysis, the technology is modelled to affect costs by: • **Decreasing drug acquisition costs** because the costs for fedratinib are lower than the costs for BAT due to the high drug wastage assumed for suboptimal ruxolitinib in BAT."	This statement infers there has been a change in the fedratinib acquisition cost due to wastage which is not factually correct. Please consider amending to the following: "Accounting for the additional costs from wastage associated with ruxolitinib administration which in turn increases the acquisition cost for ruxolitinib. This results in a lower acquisition cost for fedratinib compared to BAT."	This is factually incorrect as it infers fedratinib's acquisition costs have decreased by accounting for wastage. This is not the case, fedratinib acquisition cost is not affected by wastage.	The EAG does not consider that the statement is likely to be interpreted in the manner the company suggests and therefore it is not factually inaccurate. However, as the company has raised this concern, the statement has been reworded to try to make it clearer that the 'decreasing drug acquisition costs' relate to the difference in total drug costs for the fedratinib arm versus total drug costs for the BAT comparator arm, with the latter being high due to the drug wastage assumption for ruxolitinib.

Issue 2 Inaccurate wording related to patients with absolute neutrophil count (ANC) below 1.0 x 10^9/L or a platelet count below 50 x 10^9/L.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Section 2.3.2. (page 25), the EAG report states: "Treatment initiation is not recommended in patients with an absolute neutrophil count (ANC) below 1.0 x 10^9/L or a platelet count below 50 x 10^9/L.[14]"	The sentence should read: "Treatment initiation is not studied in patients with an absolute neutrophil count (ANC) below 1.0 x 10^9/L or a platelet count below 50 x 10^9/L.[14]"	It is factually inaccurate to state that treatment initiation is not recommended in patients with an absolute neutrophil count (ANC) below 1.0 x 10^9/L or a platelet count below 50 x 10^9/L. The CS states that treatment initiation is not studied in the population described above.	The EAG does not consider this to be a factual inaccuracy. The SPC (page 2) states "*Initiating treatment with Inrebic is not recommended in patients with a baseline platelet count below 50 x 10^9/L and ANC < 1.0 x 10^9/L."* The text in the EAG report has been amended to reproduce the text in the SPC exactly to reduce the possibility of a different interpretation being implied by the use of slightly different wording.

Issue 3 Inaccurate wording related to what appears in the SACT report.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Section 3.2.3. (page 37), the EAG report states: "However, for OS in SACT, the CS cites a data cut-off of 5 February 2024 and a median follow-up of 15.5 months; this later data cut for OS is presented in the CS but does not appear in the SACT report."	The sentence should read: "A reassessment of vital status was performed on 5 February 2024; the median follow-up time was then 15.5 months (471 days)."	It is factually inaccurate to state that the later data cut for OS is presented in the CS but does not appear in the SACT report. It does appear in the review dated 190224 (8. Addendum)	The EAG thanks the company for providing the version of the SACT report with the relevant addendum describing the later data cut along with their factual accuracy check form. Having now checked the data against the newly provided addendum, the EAG is happy to amend the text as suggested to reflect the additional details provided in the addendum to the SACT report.

Issue 4 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Section 1.6 Table 2 (page 21), the EAG report states in row EAG EA5: "-£[redacted]"	Correct number: "£[redacted]"	Difference from the company BC. The difference is not rounded up to the correct number (minor, due to decimals in the INMB)	Amended as suggested.
In Section 1.6 Table 2 (page 21), the EAG report states in row EAG EA5: "-£[redacted]"	Correct number: "-£[redacted]"	The incremental cost is not correct.	Corrected as suggested
In Section 1.6 Table 2 (page 21), the EAG report states in row EAG SA 2: "[redacted]"	Correct ICER: £[redacted]	The ICER is not correct.	Corrected as suggested
In Section 2.3.2. (page 26), the EAG report states: "The list price for fedratinib is £6,199.68 for 120 capsules"	The sentence should read: "list price for fedratinib is £6,119.68 for 120 capsules"	The current price is incorrect	Corrected as suggested

<table>
<tr>
<td>In Section 3.2.6 (page 40), the EAG report states: “Reasons for discontinuation are shown in Table 6.” The results are shown in Table 8.</td>
<td>The sentence should read: “Reasons for discontinuation are shown in Table 8.”</td>
<td>The current table reference is incorrect.</td>
<td>Corrected as suggested</td>
</tr>
<tr>
<td>In Section 3.2.6, Table 8 (page 41), the EAG report states:
<table><tr><th>N (%)</th><th>Fedratinib (N=134)</th><th>BAT (incl crossover to fedratinib) (N=67)</th><th>BAT (before crossover) (N=67</th><th>BAT to Fedratinib (after crossover) (N=46)</th></tr><tr><td>Crossed over to fedratinib</td><td>-</td><td>-</td><td>46 (69)</td><td>-</td></tr></table>
The number of patients crossed over to fedratinib should be included in the column labelled ‘BAT (incl crossover to fedratinib)’.</td>
<td>The table should look as follows:
<table><tr><th>N (%)</th><th>Fedratinib (N=134)</th><th>BAT (incl crossover to fedratinib) (N=67)</th><th>BAT (before crossover) (N=67</th><th>BAT to Fedratinib (after crossover) (N=46)</th></tr><tr><td>Crossed over to fedratinib</td><td>-</td><td>46 (69)</td><td>-</td><td>-</td></tr></table></td>
<td>The current reporting of patients crossed over to fedratinib from BAT is incorrect.</td>
<td>The EAG has reconsidered the labelling in this table. The middle of the three columns for BAT is now labelled “BAT (excl. crossover) (N=21)” as it provides the disposition of the 21 patients enrolled and treated in the BAT arm who did not crossover to fedratinib. The row “Crossed over to fedratinib” has been deleted.</td>
</tr>
<tr>
<td>In Section 3.2.7, Table 9 (page 43), there is a typo. The EAG report states:
<table><tr><th></th><th>FREEDOM-2</th><th>SACT</th></tr></table></td>
<td>Correct the characteristic to ‘Median baseline spleen volume, mL (range).</td>
<td>The current label for this characteristic is incorrect.</td>
<td>Corrected as suggested</td>
</tr>
</table>

<table><tr><th>Characteristic</th><th>Fedratinib (N=134)</th><th>BAT (N=67)</th><th>Fedratinib (N=54)</th></tr><tr><td>(IR</td><td>2,622 (498-8,909)</td><td>2,693 (383-8,515)</td><td>-</td></tr></table> The characteristic is labelled as '(IR' but is referring to median baseline spleen volume.			
In Section 3.3.2 (page 47), the EAG report states: "larger treatment effect was observed in the subgroup with lower baseline platelet counts (50 to 100 × 10^9/L)". The subgroup is actually defined as 50 to <100 × 10^9/L.	The section of this sentence should read: "larger treatment effect was observed in the subgroup with lower baseline platelet counts (50 to <100 × 10^9/L)".	The current definition of the subgroup is incorrect.	Amended as suggested
In Section 3.3.4, Table 15 (page 50), there is a typo. The EAG report states: <table><tr><th rowspan="2">Outcome</th><th colspan="4">FREEDOM-2</th></tr><tr><th colspan="2">Fedratinib</th><th colspan="2">BAT</th></tr><tr><th>N</th><th>Median</th><th>N</th><th>Median</th></tr><tr><td>Durability of symptom response (time from first ≥ 50% TSS reduction to first documented TSS reduction <50%)</td><td>90</td><td>12 weeks (2.8 months)</td><td>23</td><td>10 weeks (2.3 months)</td></tr></table> And in Section 3.3.5 (page 50), the EAG report states: "while in the BAT arm, 23 (48%) had a symptom response at any time".	Correct the N for BAT to 32 patients.	The current value is incorrect.	Corrected as suggested

The N for BAT is reported in CS Section B.2.6.1.4 (Figure 8, page 38) as N = 32.			
In Section 3.4.3 (page 62), the EAG report states: “Grade 3 or 4 AEs were reported in 76% and 67% with fedratinib (all-treated and crossover) and 55% with BAT”. The CS Table 27 reports 76.9% of grade 3 or 4 AEs were reported in the fedratinib all-treated group.	Correct 76% to 77%.	The current value is incorrect.	Corrected as suggested.
In Section 4.2.5.5.3, Table 31 (page 92), the EAG report states: Cost per week, 12-24 weeks presents a cost of £145.69	The cost should be presented as: £145.96	The current cost is incorrect	The number in the model is actually £145.69 so this has not been amended, but a footnote has been added to highlight the discrepancy with CS, Table 70.
In Section 6, (page 134). The INMB presented is not correct and NOT aligned with previous results presented: “This has a substantial impact on the INMB (when valuing a QALY at £20,000), decreasing it to £[redacted] (from £[redacted]) when applied as a single change to the company’s base-case.”	Correct INMB: “This has a substantial impact on the INMB (when valuing a QALY at £20,000), decreasing it to £[redacted] (from £[redacted]) when applied as a single change to the company’s base-case.”	The current INMB presented is incorrect.	Corrected as suggested.

Issue 5 Error in interpretation of shorter OS in SACT

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Section 3.3.8 (page 55), the EAG report states: "The EAG queried why OS in SACT might be shorter than OS in the FREEDOM-2 fedratinib arm. The company responded (clarification response, question A26) that the SACT dataset includes older patients than FREEDOM-2 (though the EAG does not agree that this can be determined from the baseline data), that SACT has more male patients (76% in SACT, 56% in FREEDOM-2), and that the treatment duration is shorter in SACT than FREEDOM-2.17 However, the EAG considers that none of these factors adequately explain the difference in OS".	The company proposes all justification for shorter OS in the SACT verses the FREEDOM-2 fedratinib arm be included in the report and incorporated into the EAG interpretation.	The current wording does not include all the possible factors considered by the company.	The EAG has added the following sentence, "*The company also noted that ECOG PS was missing for a substantial proportion of the SACT dataset (48%), making it difficult to compare disease burden, and that real-world studies carry higher uncertainty.*"

Additional factors to consider were included within the clarification response, question A26. Including the performance status of 48% of the SACT population was missing and real-world evidence carries higher uncertainty and thus has lower confidence than evidence gathered in a clinical trial setting.			

Issue 6 Error in interpretation of Health-related quality of life analysis

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Section 3.3.10 (page 59), the EAG report states: "The EORTC QLQ-C30 measures various domains on a 0-100 scale where a 10-point change is considered clinically meaningful (according to the CS)." The statement suggests the company have decided the	We propose the removal of "(according to the CS)" and revise the sentence to: "The EORTC QLQ-C30 measures various domains on a 0-100 scale where a 10-point change is considered clinically meaningful."	To ensure accurate interpretation of the analysis method used.	Amended as suggested

clinically meaningful threshold. However, CS Section B.2.6.1.4 (page 41) states: “A ≥ 10-point change, as reported by Osoba et al., has been commonly used as a threshold to define a meaningful change at a group level (i.e., within-group change and between-group difference). To aid in interpretation, this threshold was used to highlight clinically meaningful change in the mean change from baseline.”. Therefore, showing this is a recognised threshold and an appropriate analysis method.			

Issue 7 Error in description of treatment-related safety analysis

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Section 3.4.3 (page 62), the EAG report states: "AEs leading to death were reported in 16% and 9% with fedratinib (all-treated and crossover) and 6% with BAT (there was no analysis of treatment-related AEs leading to death)." The statement here suggests no analysis was performed for treatment-related AEs leading to death. However, clarification response, question A27 describes the process for reporting treatment-related AEs.	We propose the following amendment: "AEs leading to death were reported in 16% and 9% with fedratinib (all-treated and crossover) and 6% with BAT (there were no reported treatment-related AEs leading to death)."	The EAG report text reads as no analysis however there was a procedure for assigning treatment-related AEs and therefore no treatment-related AEs leading to death were reported.	The EAG notes that the company response to A27 states "*AEs leading to death were reported as treatment-emergent; AEs leading to death that were treatment-related were not considered as an analysis.*" This is why the EAG was unsure if these events were not analysed or if none were reported. However, the EAG understands from the company's FAC response that no treatment-related AEs leading to death were reported. Therefore the text is amended as suggested.

Issue 8 Missing information

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Section 3.4.4 (page 62), the EAG report states: "In the BAT group (no crossover), the most common AEs were anaemia (36%), asthenia (24%), thrombocytopenia (18%) and nausea (15%)." However, CS Tables 28 also states the AEs fatigue and pruritus also reported 15% in the BAT group.	Reword to: "In the BAT group (no crossover), the most common AEs were anaemia (36%), asthenia (24%), thrombocytopenia (18%), nausea (15%), fatigue (15%) and pruritus (15%). "	To ensure accuracy in the EAG report.	Have amended text to include pruritus and fatigue.
In Section 3.4.4, Table 17 (page 63), the EAG report reports: common treatment-emergent AEs of ≥15%. The CS Table 29 also reports AEs of night sweats and abdominal pain as greater than 15% in the crossover population.	Add data for night sweats and abdominal pain as an additional row in Table 17.	To ensure accuracy in the EAG report.	Amended Table 17 to add data for night sweats and abdominal pain
In Section 3.4.4, Table 17 (page 63), the EAG report	Add data for pneumonia and renal failure as an additional row in Table 17.	To ensure accuracy in the EAG report.	Amended Table 17 to add data for pneumonia and renal failure

reports: common treatment-related AEs of ≥5%. The CS Table 29 also reports AEs of pneumonia and renal failure as greater than 5% in the crossover population.			
In Section 3.4.5, Table 18 (page 64), the EAG report reports: grade 3/4 treatment-related AEs ≥3%. The company's clarification response Table 7 also reports urinary tract infection as an AE in greater than 5% of the crossover population.	Add data for urinary tract infection as an additional row in Table 18.	To ensure accuracy in the EAG report.	Amended Table 18 to add data for urinary tract infection

Issue 9 Minor amendment – economic section

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.3.2, p 109. "The EAG notes that EQ-5D-5L utility values were available from the FREEDOM-2 trial and a reference case scenario using these values	The following clarification should be implemented: "The EAG notes that EQ-5D-5L utility values were available from the FREEDOM-2 trial and a reference case scenario using these values has not been provided by the	Clarification why the EQ-5D was not used	This statement is not factually inaccurate. This statement appears in a summary table and a fuller discussion of this issue is provided later in

has not been provided by the company despite this being requested during clarification." The company believes that NICE agreed that MF-8D was more relevant than EQ-5D in MF.	company based on precedent use of MF-8D in MF appraisals as being the most relevant instrument to quantify changes in health-related quality of life in MF."		the report. The EAG has added the following text to refer the reader to the later discussion: "This issue is further discussed in Section 4.3.3.9."
Section 4.4.2.5 p. 127 "EAG used the average initial dose distribution across the first 6 cycles in its base-case (equivalent to a mean daily dose of 23.8 mg) with an assumption of 5% wastage for dose adjustments". The EAG is using a value that is not the mean initial dose recorded in the CSR, but rather a lower mean dose calculated based on the average number of patients receiving each dose.	The following clarification should be implemented "EAG calculated the weighted average initial dose distribution across the first 6 cycles in its base-case (equivalent to a mean daily dose of 23.8 mg) with an assumption of 5% wastage for dose adjustments"	Clarification	Not a factual inaccuracy. The EAG do not claim to be using the mean initial dose recorded in the CSR (24.1 mg). This is why we specifically describe using the "*average initial dose distribution across the first 6 cycles*" and why we indicate that this would be equivalent to a mean daily dose of 23.8 mg. The EAG is satisfied that the text accurately describes its methods. No amendment to the report.
Section 4.3.3.2 p. 112 "The EAG notes that allowing patients to have suboptimal	As outlined in the response to clarification questions B6 and B8, suboptimal use of fedratinib is unlikely	Clarification	The EAG was intending to convey that whilst the consequence of this is

fedratinib in the model…this potentially provides better agreement with the use of fedratinib in clinical practice."	in clinical practice. Hence the text "this potentially provides better agreement with the use of fedratinib in clinical practice" should be removed		an extended fedratinib duration compared with FREEDOM-2, this is likely to provide better agreement with clinical practice, because use in clinical practice is not restricted to use up until disease progression. Text has been amended to make this clearer. It now says *"…better agreement with the use of fedratinib in clinical practice, where treatment is not required to stop on disease progression*."
Section 4.3.3.3 p. 113 "An alternative method to correcting this inconsistency would be to…"	The described approach reflects the differences in available treatments for patients receiving either fedratinib or BAT, and is neither an inconsistency nor an error that needs correcting. Hence the sentence should be re-worded as: "An alternative method would be to…"	Clarification	The inconsistency is that non-responders to fedratinib are allowed to receive subsequent BAT, whereas patients receiving ruxolitinib as BAT in the comparator arm are not allowed to receive subsequent BAT if they do not respond to ruxolitinib. The EAG has

			amended the previous paragraph to make this inconsistency clearer by adding, "*because one group is assumed to be eligible for subsequent treatment with non-JAK inhibitor forms of BAT and the other is no*t."
Section 4.3.3.5 p. 114 "This is because the company's approach to estimating the dosing of ruxolitinib results in an average daily dose of [redacted] mg per patient, which is much higher than the mean dose per patient reported in the CS of 24.1 mg"	It is worth noting that the approach taken in the CS accounts for the frequently observed dose changes in FREEDOM-2 so would be a more accurate estimate of the ruxolitinib costs.	Clarification	This is not a matter of factual inaccuracy. The EAG report section 4.3.3.5 already provides a full discussion of this issue including a description of "*frequent requirements for dose adjustments within the trial population…"* a few sentences later. No amendment has been made.
Section 4.3.3.10 p. 118 "…the EAG calculates from the model that the average number of RBC units transfused in those on treatment with fedratinib will	Text provided is inconsistent; a higher rate is given for fedratinib (29.33 vs 28.89) but this is then stated to be 5% lower. This discrepancy should be amended.	Typo	Discrepancy has been amended to say "model predicts 2% higher RBC transfusion units in the fedratinib arm than in the BAT arm over the

be 29.33 units over 144 weeks, whereas the average number of units for those on treatment with BAT will be 28.89 units over 144 weeks...Therefore, the model predicts 5% lower RBC transfusion units in the fedratinib arm than in the BAT arm over the first 144 weeks of treatment"			first 144 weeks of treatment." Remaining text in paragraph unchanged as 2% higher is still inconsistent with 37% higher.
Section 4.3.3.14 p122-123: "The CS states that "*the option to pool fedratinib and BAT together*…The EAG is concerned that the company has explored multiple approaches to extrapolating OS and TTD without applying a consistent and logical rationale throughout the whole process."	The examples cited to support this assertion conflate the justification for the base-case (which pools outcomes by treatment, informed by clinical advice that crossing of the survival curves was unlikely) with the justification for the scenarios which consider treatment-specific survival.	Clarification	The EAG is citing these examples to illustrate the inconsistency in the assumptions applied across the different scenarios presented by the company, including their basecase scenario. Therefore this is not factually inaccurate and no amendment has been made.

Issue 10 Minor amendment - editorial

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.5.5.4, p. 93. Wrong termination of the verb: "A cost of £44 per test is assumed from NHS Reference Costs 2021-22 with 23.13% of patients requiring thiamine base on FREEDOM-2."	Correcting the verb: A cost of £44 per test is assumed from NHS Reference Costs 2021-22 with 23.13% of patients requiring thiamine based on FREEDOM-2.	Typo	Amended as suggested
Section 4.3.3.6, p. 114. Typo: "[…] EAG has conducted as scenario analysis in which it applied the TTD and OS curves fitted to the BAT cohort […]"	EAG has conducted a scenario analysis in which it applied the TTD and OS curves fitted to the BAT cohort	Typo	Amended as suggested
Section 4.3.3.13, p. 120. Typo "[…]the EAG does not consider that the company's rationale for using this combined definite is reasonable given that it relies on the clinical advice […]"	However, the EAG does not consider that the company's rationale for using this combined definition is reasonable given that it relies on the clinical advice that these two measures track each other	Typo	Amended as suggested