

**Single Technology Appraisal**

**Fedratinib for disease-related  
splenomegaly and symptoms in  
myelofibrosis [ID1501]**

**Committee Papers**

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**SINGLE TECHNOLOGY APPRAISAL**

**Fedratinib for disease-related splenomegaly and symptoms in myelofibrosis  
[ID1501]**

**Contents:**

The following documents are made available to consultees and commentators:

- 1. Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**
- 2. Comments on the Appraisal Consultation Document from Celgene, a BMS company**
  - a. ACD comments form
  - b. ACD comments appendix
- 3. Consultee and commentator comments on the Appraisal Consultation Document** from:
  - a. Leukaemia Care
  - b. MPN Voice
- 4. Comments on the Appraisal Consultation Document from experts:**
  - a. Claire Harrison – clinical expert, nominated by Celgene, a BMS company
- 5. Evidence Review Group critique of company comments on the ACD**

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

# Fedratinib for treating disease-related splenomegaly or symptoms in myelofibrosis

## Single Technology Appraisal

### Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

#### Type of stakeholder:

**Consultees** – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

**Clinical and patient experts and NHS commissioning experts** – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

**Commentators** – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

**Public** – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

**Please note:** Comments received in the course of consultations carried out by NICE 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 submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee	MPN Voice	Patients for whom ruxolitinib fails or has failed to be effective have no other treatment options and their prognosis is very poor. Fedratinib has been demonstrated to be of value in terms of quality of life for these patients and it therefore meets a very significant unmet need owing to the complete lack of any other treatment options. We are concerned that the unique value that the drug represents to this patient group has been underestimated in the appraisal.	Comment noted. The committee acknowledged that disease symptoms will usually return for people having suboptimal ruxolitinib, and that when ruxolitinib is no longer suitable there are no other options other than best available therapy. The committee agreed that patients and clinicians would welcome a new treatment option for myelofibrosis, particularly when ruxolitinib is no longer suitable. Please see section 3.2 of the FAD.
2	Consultee	MPN Voice	We are also concerned that the clinician experts' opinions regarding the survival benefits of fedratinib have not been properly understood, or accounted for, in the appraisal. The experts have pointed out that the proven benefit that the drug demonstrates in terms of symptom reduction, especially reduction of spleen size, is almost certainly reflected in extended survival of the patients in question. Admittedly, the trial data presented to date does not explicitly prove this, but the opinion of the world's leading MPN experts is clear in this respect and does not appear to have been properly acknowledged in the appraisal.	Comment noted. The views of clinical experts were considered by the committee when formulating its recommendations. The committee heard from clinical experts that there is real-world and clinical trial evidence linking spleen response to overall survival, and that it was implausible that fedratinib would have no overall survival benefit over best available therapy. The committee considered that fedratinib was likely to extend overall survival. However, the committee was also aware that in an exploratory MAIC for overall survival using evidence from JAKARTA-2 and SIMPLIFY-2, the overall survival for people having fedratinib was similar to that for people having best available therapy after matching based on DIPSS risk category. After adjusting for other prognostic factors such as platelet count and transfusion dependence in the MAIC, people having fedratinib had a shorter overall survival than those having best available therapy. The committee concluded that based on the evidence

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				presented, the extent of the overall survival benefit for fedratinib was highly uncertain. Please see section 3.11 of the FAD.
3	Consultee	MPN Voice	<p>Myelofibrosis is, thankfully, a rare disease. Within the small number of MF patients, only an even smaller subset is in the category of ‘post-ruxolitinib’ treatment. It is therefore understandable that limited data is available for the type of full cost-benefit analysis that NICE would normally expect to perform. But the comparative lack of data is only due to the rarity of the disease and does not affect either (a) the effectiveness of the drug or (b) the unique benefit that it provides to patients for whom all other therapies have failed.</p> <p>We believe, therefore, that ‘post-rux’ MF patients are being unfairly treated by this decision on the basis of the rarity of their situation.</p>	Comment noted. The committee acknowledged the difficulty of collecting data for rare diseases. It concluded that fedratinib is clinically effective, but that the disruption to the trial and lack of comparative data made the assessment of comparative effectiveness challenging. Please see section 3.6 of the FAD.
4	Consultee	MPN Voice	We understand that further data regarding both the symptom reduction and the survival benefit of fedratinib will be published as part of the FREEDOM2 trial. We therefore urge the committee to revisit the appraisal at the earliest opportunity once the data has been published.	Comment noted. The committee considered that FREEDOM-2 would likely resolve some of the modelling uncertainties. These included the extent of a fedratinib survival benefit compared with best available therapy and the ruxolitinib treatment costs (how many people have the lower dose of ruxolitinib in the setting of best available therapy). The committee concluded that fedratinib met the criteria for inclusion in the Cancer Drugs Fund. Please see section 3.21 of the FAD.
5	Consultee	MPN Voice	We understand that the pricing of the drug is an important factor in the committee’s decision not to recommend fedratinib. However, in light of the concerns we have outlined above, we believe that there remains a strong argument for fedratinib to be made available to patients for whom no other effective treatment is available via the Cancer Drugs Fund. We therefore ask the committee to reconsider whether that option should be provided for these patients.	Comment noted. The committee considered whether the remaining uncertainties in the company’s modelling could be addressed through collecting more data within the Cancer Drugs Fund. It noted that FREEDOM-2 would likely resolve some of the modelling uncertainties. These included the extent of a fedratinib survival benefit compared with best available therapy and the ruxolitinib treatment costs (how many people have the lower dose of ruxolitinib in the setting of best available therapy). Using fedratinib in the NHS would also allow data to be collected using the Systemic Anti-Cancer dataset. This would provide data on overall survival and treatment duration for people having fedratinib in clinical

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				practice. The committee concluded that fedratinib met the criteria for inclusion in the Cancer Drugs Fund. Please see section 3.21 of the FAD.
6	Consultee	Leukaemia Care	We would like to reiterate the significant unmet need in this population. The group in whom ruxolitinib is no longer effective have a poor prognosis and most continue on an ineffective treatment or have only palliative care. As per our previous submissions, this treatment improves the quality of life for these patients as well as improving their survival.	Comment noted. The committee acknowledged that when ruxolitinib is no longer suitable there are no other options other than best available therapy. It agreed that patients and clinicians would welcome a new treatment option for myelofibrosis, particularly when ruxolitinib is no longer suitable. Please see section 3.2 of the FAD.
7	Consultee	Leukaemia Care	Whilst we appreciate there are concerns about the clinical trial data, part of the reason that there is limited data on this treatment is due to the rarity of myelofibrosis. The STA process requires a body of evidence that is more difficult to collect in rare conditions, which is unfair for illnesses. This group of rare illnesses, yet not so rare as to qualify for HST, are unfairly disadvantaged by this process. Therefore, we feel the committee accept a higher degree of uncertainty than it is currently.	Comment noted. The committee acknowledged the difficulty of collecting data for rare diseases. Please see section 3.6 of the FAD.
8	Consultee	Leukaemia Care	Trials are ongoing for this treatment, including the FREEDOM2 trial. Therefore, we ask that the committee consider this treatment for the Cancer Drugs Fund to resolve some of the uncertainties. The trial should not be dismissed due to the crossover in the FREEDOM2 trial, as this can be accounted for.	Comment noted. The committee considered that FREEDOM-2 would likely resolve some of the modelling uncertainties. These included the extent of a fedratinib survival benefit compared with best available therapy and the ruxolitinib treatment costs (how many people have the lower dose of ruxolitinib in the setting of best available therapy). The committee concluded that fedratinib met the criteria for inclusion in the Cancer Drugs Fund. Please see section 3.21 of the FAD.
9	Consultee (company)	Celgene, a BMS Company	Fedratinib has not been recommended for use in the Cancer Drugs Fund.  The committee considered that while FREEDOM-2 1 would likely resolve some of the modelling uncertainties, it may not robustly resolve the uncertainty around a fedratinib survival benefit because crossover is allowed at 6 months (or earlier with disease progression). It is important to note that crossover can and has been handled by NICE previously on several occasions, including in the assessment of ruxolitinib (TA386)2, and is a feature common to prior (e.g. PERSIST-2, SIMPLIFY-2)3, 4, and ongoing trials (e.g. Imetelstat study for patients who have not responded to a JAK-Inhibitor - NCT04576156; LIMBER-313) in myelofibrosis that	Comment noted. The committee acknowledged that when ruxolitinib is no longer suitable there are no other options other than best available therapy. It agreed that patients and clinicians would welcome a new treatment option for myelofibrosis, particularly when ruxolitinib is no longer suitable. Please see section 3.2 of the FAD.  The committee considered whether the remaining uncertainties in the company's modelling could be

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			<p>should not prevent assessments of survival being made</p> <p>The Cancer Drugs Fund would not only resolve key uncertainties in modelling inputs (such as prior treatment, response outcomes, discontinuation rate and composition of BAT for those who discontinue fedratinib), but both FREEDOM-2 and the Cancer Drugs Fund could provide valuable information on survival benefit despite crossover and the real world discontinuation rate.</p> <p>This is particularly important for a patient group with high unmet need; where fedratinib is currently the only licensed product available for patients previously treated with ruxolitinib, and this landscape is not expected to change within the next 2 years. Additionally, fedratinib has been proven as clinically effective treatment (as described at the committee meeting by a patient who had received fedratinib and by the who have or are currently participating in fedratinib clinical trials), and the committee considered that fedratinib was likely to extend overall survival.</p> <p>Therefore, the company believe that making fedratinib available through the CDF would allow patients with a high unmet need have access to another effective therapy, whilst addressing the uncertainties the committee have raised.</p>	<p>addressed through collecting more data within the Cancer Drugs Fund. It noted that FREEDOM-2 would likely resolve some of the modelling uncertainties. These included the extent of a fedratinib survival benefit compared with best available therapy and the ruxolitinib treatment costs (how many people have the lower dose of ruxolitinib in the setting of best available therapy). Using fedratinib in the NHS would also allow data to be collected using the Systemic Anti-Cancer dataset. This would provide data on overall survival and treatment duration for people having fedratinib in clinical practice. The committee concluded that fedratinib met the criteria for inclusion in the Cancer Drugs Fund. Please see section 3.21 of the FAD.</p>
10	Consultee (company)	Celgene, a BMS Company	<p>The company acknowledges the review of the ERG and the discussion of the committee.</p> <p>As such, the following assumptions have been updated in revised cost-effectiveness analysis.</p> <ol style="list-style-type: none"> <li>1. 65% of initial responders to fedratinib are assumed to continue fedratinib within best available therapy. This is described in further detail in comment 5.</li> <li>2. The rate of transformation to acute myeloid leukaemia should be consistent between treatment arms, in the absence of significant evidence otherwise, informed by COMFORT-II <sup>5</sup> data.</li> </ol> <p>The introduction of the above assumptions and the proposed increased confidential discount to the list price of fedratinib, results in an ICER of £18,294.</p>	<p>Comment noted. The committee was aware of the company's revised assumptions. It acknowledged both updates in sections 3.13 and 3.14 of the FAD, respectively.</p>

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11	Consultee (company)	Celgene, a BMS Company	<p>For end-of-life criteria to be met, it is first required that current life expectancy be less than 24 months.</p> <p>The clinical experts at the committee meeting explained that life expectancy for people who stop ruxolitinib is around 12 to 18 months. The committee was also aware that median overall survival after stopping ruxolitinib was 16 months or less in COMFORT-II, Schain and based on the HMRN data.</p> <p>In Technology Appraisal 386 (TA386, <i>“Ruxolitinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis”</i>)<sup>2</sup>, the committee concluded that the high-risk population met end-of-life criteria. On this basis, it can be expected that survival of less than 24 months would hold for at least 42% of the modelled population who are high-risk and R/R/I to ruxolitinib.</p> <p>The committee papers for this appraisal present the mean life expectancy from the company base case model as a basis to reject this end-of-life criterion. This is higher than the <i>median</i> life expectancy in the company base case model of [REDACTED] months, due to the long tail of the chosen survival extrapolation, which is likely to be optimistic. For the majority of patients it is expected that they would live for less than 24 months, however there will be outliers. At 24 months in the model, only 38.5% of patients are alive in the best available therapy arm, as opposed to 54.0% in the fedratinib arm.</p> <p>Other clinically plausible extrapolations of the comparator data (such as the exponential distribution) would yield mean survival of &lt; 24 months (1.92 life years, 34.2% patients alive at 24 months).</p> <p>The Kaplan-Meier data for most evidence sources in the economic model have a long tail, driven by censoring and low numbers at risk. The mean life expectancy can only be appropriately calculated from mature KM data; and therefore, median survival is likely to be a more appropriate measure in this instance to inform life expectancy for end-of-life criteria.</p> <p>Overall, we are concerned that the recommendation may not fairly reflect the survival burden of patients who have been previously treated with ruxolitinib, have become relapsed/refractory or intolerant and are further</p>	<p>Comment noted. The committee considered the company’s comments at the second committee meeting. The committee was concerned that the population in Schain, where people had stopped ruxolitinib treatment, did not reflect the modelled best available therapy arm, where most people continued ruxolitinib treatment (see sections 3.10 and 3.11 of the FAD). It noted additional uncertainty in the clinician estimates that informed the choice of survival model for people having best available therapy. It would have preferred to see a scenario with a survival model fitted directly through the clinician estimates. As this would lie above the exponential distribution (which gave a mean survival of 23.3 months), the committee considered that it was likely this scenario would give a mean survival of more than 24 months.</p> <p>The committee also noted that because the cost-effectiveness results are calculated based on mean (rather than median) numbers, it is important to consider the mean survival results when assessing whether the end of life criteria were met. Please see section 3.17 of the FAD.</p> <p>The committee also noted that baseline characteristics from a global chart review were provided to support the argument that people having best available therapy have poor survival outcomes. Please see section 3.15 of the FAD.</p>



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			<p>along in their disease course</p> <p>Poor survival outcomes in current practice were observed in the global chart review outlined during Technical Engagement. Baseline characteristics have been provided in an appendix showing similarities to the JAKARTA-2 population.</p>	
12	Consultee (company)	Celgene, a BMS Company	<p>For end-of-life criteria to be met, it is also required that fedratinib provide an expected extension to life of <math>\geq 3</math> months.</p> <p>The committee considered that fedratinib was likely to extend overall survival. However, it concluded that based on the evidence presented, the extent of this overall survival benefit was highly uncertain.</p> <p>JAKARTA-2 showed that the proportion of patients with spleen response was [REDACTED] (unadjusted data for intermediate-2 and high-risk patients), which was significantly higher than the SIMPLIFY-2 and PERSIST-2 BAT response in both the naïve comparison and in the indirect treatment comparisons. There is a wealth of published evidence investigating the relationship between survival and spleen size in myelofibrosis patients. 12 identified studies examining this relationship were presented in Appendix L.7. of the original submission. Of the 7 studies that investigated the relationship between change in spleen length, size or volume (with varying definitions of response threshold) and overall survival, all 7 found that spleen response was associated with positive survival outcomes in the investigative arm. 4 of the 7 studies presented hazard ratios to quantify the relationship:</p> <ul style="list-style-type: none"> <li>• Vannucchi et al. 2015 <sup>6</sup> - Evidence in the investigative arm supporting both spleen volume reduction (HR = 0.24) and spleen length reduction (HR = 0.28) having association with survival. Results not replicated in control arm (low number of responders)</li> <li>• Verstovsek et al. 2012 <sup>7</sup> - Patients who experienced a confirmed <math>\geq 50\%</math> reduction in palpable spleen size (n = 61) had significantly prolonged survival compared with the minority of patients (n = 23) with a <math>&lt; 25\%</math> reduction in spleen from baseline (HR = 0.223; 95% CI, 0.097-0.512; P = .0001)</li> <li>• Mesa et al. 2016 <sup>8</sup> - Relative to patients who did not respond (<math>&lt; 10\%</math> SVR), those with a response (<math>\geq 35\%</math> SVR) had a hazard ratio of 0.294. Results not replicated in BAT arm (low number of responders)</li> </ul>	<p>Comment noted. The committee considered the survival evidence presented for people having fedratinib compared with people having best available therapy. It also considered the input of clinical experts at the first committee meeting and the use of spleen response as a surrogate for survival. However, the committee noted that the company's base case did not use spleen response as a survival surrogate. The committee considered that it had not seen sufficient evidence to change its conclusion from the first meeting. It felt that fedratinib was likely to extend overall survival compared with best available therapy. However, it concluded that based on the evidence presented, the extent of this overall survival benefit was highly uncertain. Please see section 3.11 of the FAD.</p>

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			<ul style="list-style-type: none"> <li>Petti et al. 2002<sup>9</sup> - Response predictive of overall survival. In multivariate analysis, not achieving any type of response, either partial or complete, was associated with a HR of 3.9.</li> </ul> <p>This evidence is wholly supportive of a link between spleen response and survival benefit. Fedratinib has been shown to provide meaningful spleen response in a population relapsed, refractory or intolerant to ruxolitinib. Although there is uncertainty, the company have taken a conservative approach on estimating survival, which leads to an estimated survival that is greater than 3 months for fedratinib compared to BAT. Therefore, the company believe that both criteria for end-of-life would be met.</p>	
13	Consultee (company)	Celgene, a BMS Company	<p>The company base case model assumed that people having fedratinib would discontinue after disease relapse.</p> <p>The committee felt that most people are likely to keep having fedratinib after losing disease response, although the proportion who will do so is uncertain.</p> <p>It was considered that the proportion of people who would continue treatment with fedratinib was uncertain and would likely be between the estimates of a company scenario (65%) and the ERG scenario (89%).</p> <p>In JAKARTA-2, prior to the clinical hold, 35% of patients had discontinued fedratinib. This would suggest that estimates of patients continuing long-term fedratinib greater than 65% would not be reasonable. The discontinuations comprised 18 patients (19%) due to AEs, six (6%) due to disease progression, three (3%) because of patient decision and seven (7%) for other reasons. The company expect that the proportion of patients who continue would only include those who initially responded to fedratinib. In revised cost-effectiveness analysis, it is assumed that 65% of responders continue fedratinib beyond the initial extrapolated time of discontinuation. This was supported with the clinicians surveyed by the company when asked this question.</p> <p>Early interim real-world data from the United States, where fedratinib has been licensed for treating myelofibrosis in patients who are JAKi naïve or have been previously treated with ruxolitinib since August 2019, indicates an observed discontinuation rate of ■ over the current study period. This does suggest the company assumptions is likely to be an overestimate for</p>	<p>Comment noted. The committee considered the proportion of people on fedratinib who would continue having it after their disease stopped responding. It considered the following scenarios:</p> <ul style="list-style-type: none"> <li>65% of people whose disease initially responded to fedratinib would continue having fedratinib after their disease stops responding (company's base case)</li> <li>65% of all people starting fedratinib would keep having it after their disease stops responding (ERG scenario), and</li> <li>89% of all people starting fedratinib would keep having it after their disease stops responding (ERG scenario)</li> </ul> <p>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. The committee concluded that it was appropriate to assume 89% of all people starting fedratinib would continue fedratinib after their disease stopped responding, because that was consistent with the proportion of people who were assumed to continue ruxolitinib in the best available therapy arm. Please see section 3.13 of the FAD.</p>

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			<p>the continuation of fedratinib after a loss of response.</p> <p>One aspect the company did not explore was the dose of fedratinib when continued after loss of response. For ruxolitinib, lower doses are used in clinical practice, and therefore it would be expected that lower doses of fedratinib would also be used. The company did seek clinical advice and no dose was conclusively recommended as it was difficult to state without using fedratinib in this setting. The company are suggesting a lower dose intensity would be used in line with the current practice with ruxolitinib and have suggested a ■■■ RDI in a scenario analysis.</p>	
14	Consultee (company)	Celgene, a BMS Company	<p>The company model has been described as having an overly complex model structure. There were also inconsistencies noted in modelling approach between treatment arms.</p> <p>Many of the challenges of the model structure relate to weaknesses in the dataset, that would only be overcome with more data collection, and that oversimplifying a challenging decision problem would have created separate issues.</p> <p>It was noted by the ERG that there were differences in the modelling between the treatment arms. The modelling approach between treatment arms differed partly due to data availability, and some differences were necessary to reflect how patients who receive fedratinib after ruxolitinib undergo an altered treatment pathway to those who move onto best available therapy immediately.</p> <p>Some of the uncertainty and perceived complexity arises because of separating inputs for responders from non-responders – whereas in a simpler cohort model type, inputs would be pooled, and calculations would be based on the average patient. A pooled approach using pooled data that is available and can be conducted within the existing company model, which uses consistent curves between responders and non-responders, based on a dataset covering all JAKARTA-2 intermediate-2 and high-risk patients. In such an approach, the only significant difference to a typical cohort model is that a cohort model averages the patients at the beginning and uses the cohort inputs, whereas the DES model simulates each patient as an individual and averages the outcomes at the end. Such an analysis yields highly comparable ICERs to the company base case</p>	<p>Comment noted. The committee acknowledged the company's rationale for its cost-effectiveness model structure, in that it was similar to the approach used in TA386. It noted that the company made few changes to the model presented at the first committee meeting, and that the ERG's view of the model remained unchanged. The committee concluded that a simpler model may have been more robust for decision making, given the limitations of the clinical evidence for fedratinib. Please see section 3.9 of the FAD.</p>

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			(within 2%), which supports the modelling assumptions that have been made in the submission.	
15	Consultee (company)	Celgene, a BMS Company	<p>The preferred ERG base case included settings that may not be representative of UK practice or population outcomes.</p> <p>During the TA386 process, wastage was included at the request of the ERG as they were concerned by the company assumption of no drug wastage. They noted that most adverse events are managed by dose reduction or interruption and that this would lead to additional costs. The experts during TA386 advised that assuming no drug wastage for ruxolitinib reflected its use in clinical practice. It is important to highlight that having access to the patient level data also supported the decision of no wastage. However, it is unclear whether this remains true as informal discussions with clinicians support the previous ERG assumption, which would require new packs or lead to use of multiple 5mg tablets. We therefore believe it is inappropriate to assume no ruxolitinib wastage in this submission.</p>	<p>Comment noted. The committee acknowledged the uncertainty around ruxolitinib costs, and concluded that it was appropriate to consider scenarios including and excluding drug wastage for ruxolitinib. Please see section 3.16 of the FAD.</p>
16	Clinical expert	Claire Harrison	<p>Patients for whom ruxolitinib fails or has failed to be effective have no other treatment options and their prognosis is very poor. The ERG and all experts agree this.</p>	<p>Comment noted. The committee acknowledged that when ruxolitinib is no longer suitable there are no other options other than best available therapy. It agreed that patients and clinicians would welcome a new treatment option for myelofibrosis, particularly when ruxolitinib is no longer suitable. Please see section 3.2 of the FAD.</p>
17	Clinical expert	Claire Harrison	<p>Fedratinib has been demonstrated to be of value in terms of quality of life for these patients and it therefore meets a very significant unmet need owing to the complete lack of any other treatment options. The issue of whether spleen response is linked to survival benefit was argued and disagreed with despite this being internationally accepted and accepted by other bodies eg FDA etc.</p>	<p>Comment noted. The views of clinical experts were considered by the committee when formulating its recommendations. The committee agreed that patients and clinicians would welcome a new treatment option for myelofibrosis, particularly when ruxolitinib is no longer suitable. Please see section 3.2 of the FAD.</p> <p>The committee considered that fedratinib was likely to extend overall survival. It acknowledged the clinical expert statements that there is real-world and clinical trial evidence linking spleen response to overall survival. Please see section</p>

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18	Clinical expert	Claire Harrison	Given the above and the understanding that further data regarding both the spleen and symptom reduction and the survival benefit of fedratinib will be published as part of the FREEDOM 1 and 2 trials. May I respectfully ask why the drug has not been recommended to go to the CDF pending this and other real world data?	3.11 of the FAD. Comment noted. The committee considered whether the remaining uncertainties in the company's modelling could be addressed through collecting more data within the Cancer Drugs Fund. It noted that FREEDOM-2 would likely resolve some of the modelling uncertainties. These included the extent of a fedratinib survival benefit compared with best available therapy and the ruxolitinib treatment costs (how many people have the lower dose of ruxolitinib in the setting of best available therapy). Using fedratinib in the NHS would also allow data to be collected using the Systemic Anti-Cancer dataset. This would provide data on overall survival and treatment duration for people having fedratinib in clinical practice. The committee concluded that fedratinib met the criteria for inclusion in the Cancer Drugs Fund. Please see section 3.21 of the FAD.
19	Clinical expert	Claire Harrison	Can we please understand how it is in the UK patient best interest that they do not have access to this drug?	Comment noted. Fedratinib is recommended for use within the Cancer Drugs Fund. Please see section 1.1 of the FAD.

**Fedratinib for disease-related splenomegaly and symptoms in myelofibrosis [ID1501]**

Consultation on the appraisal consultation document – **deadline for comments 5pm on Wednesday 28 July 2021**. Please submit via NICE Docs.

<p>Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.</p> <p>The Appraisal Committee is interested in receiving comments on the following:</p> <ul style="list-style-type: none"> <li>• has all of the relevant evidence been taken into account?</li> <li>• are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?</li> <li>• are the provisional recommendations sound and a suitable basis for guidance to the NHS?</li> </ul> <p>NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:</p> <ul style="list-style-type: none"> <li>• could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology;</li> <li>• could have any adverse impact on people with a particular disability or disabilities.</li> </ul> <p>Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.</p>	
<p><b>Organisation name – Stakeholder or respondent</b> (if you are responding as an individual rather than a registered stakeholder please leave blank):</p>	<p>[Celgene, a BMS Company]</p>
<p><b>Disclosure</b> Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.</p>	<p>[None]</p>
<p><b>Name of commentator person completing form:</b></p>	<p>██████████</p>
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**Fedratinib for disease-related splenomegaly and symptoms in myelofibrosis [ID1501]**

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1	<p>Fedratinib has not been recommended for use in the Cancer Drugs Fund.</p> <p>The committee considered that while FREEDOM-2 <sup>1</sup> would likely resolve some of the modelling uncertainties, it may not robustly resolve the uncertainty around a fedratinib survival benefit because crossover is allowed at 6 months (or earlier with disease progression). It is important to note that crossover can and has been handled by NICE previously on several occasions, including in the assessment of ruxolitinib (TA386)<sup>2</sup>, and is a feature common to prior (e.g. PERSIST-2, SIMPLIFY-2)<sup>3, 4</sup>, and ongoing trials (e.g. Imetelstat study for patients who have not responded to a JAK-Inhibitor - NCT04576156; LIMBER-313) in myelofibrosis that should not prevent assessments of survival being made</p> <p>The Cancer Drugs Fund would not only resolve key uncertainties in modelling inputs (such as prior treatment, response outcomes, discontinuation rate and composition of BAT for those who discontinue fedratinib), but both FREEDOM-2 and the Cancer Drugs Fund could provide valuable information on survival benefit despite crossover.</p> <p>This is particularly important for a patient group with high unmet need; where fedratinib is currently the only licensed product available for patients previously treated with ruxolitinib, and this landscape is not expected to change within the next 2 years. Additionally, fedratinib has been proven as clinically effective treatment (as described at the committee meeting by a patient who had received fedratinib and by the who have or are currently participating in fedratinib clinical trials), and the committee considered that fedratinib was likely to extend overall survival.</p> <p>Therefore, the company believe that making fedratinib available through the CDF would allow patients with a high unmet need have access to another effective therapy, whilst addressing the uncertainties the committee have raised.</p>
2	<p>The company acknowledges the review of the ERG and the discussion of the committee.</p> <p>As such, the following assumptions have been updated in revised cost-effectiveness analysis.</p> <ol style="list-style-type: none"> <li>1. 65% of initial responders to fedratinib are assumed to continue fedratinib within best available therapy. This is described in further detail in comment 5.</li> <li>2. The rate of transformation to acute myeloid leukaemia should be consistent between treatment arms, in the absence of significant evidence otherwise, informed by COMFORT-II <sup>5</sup> data.</li> </ol> <p>The introduction of the above assumptions and the proposed increased confidential discount to the list price of fedratinib, results in an ICER of £18,294.</p>
3	<p>For end-of-life criteria to be met, it is first required that current life expectancy be less than 24 months.</p> <p>The clinical experts at the committee meeting explained that life expectancy for people who stop ruxolitinib is around 12 to 18 months. The committee was also aware that median overall survival after stopping ruxolitinib was 16 months or less in COMFORT-II, Schain and based on the HMRN data.</p> <p>In Technology Appraisal 386 (TA386, “<i>Ruxolitinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis</i>”)<sup>2</sup>, the committee concluded that the high-risk population met end-of-life criteria. On this basis, it can be expected that survival of less than</p>

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	<p>24 months would hold for at least 42% of the modelled population who are high-risk and R/R/I to ruxolitinib.</p> <p>The committee papers for this appraisal present the mean life expectancy from the company base case model as a basis to reject this end-of-life criterion. This is higher than the <i>median</i> life expectancy in the company base case model of █████ months, due to the long tail of the chosen survival extrapolation, which is likely to be optimistic. For the majority of patients it is expected that they would live for less than 24 months, however there will be outliers. At 24 months in the model, only 38.5% of patients are alive in the best available therapy arm, as opposed to 54.0% in the fedratinib arm.</p> <p>Other clinically plausible extrapolations of the comparator data (such as the exponential distribution) would yield mean survival of &lt; 24 months (1.92 life years, 34.2% patients alive at 24 months).</p> <p>The Kaplan-Meier data for most evidence sources in the economic model have a long tail, driven by censoring and low numbers at risk. The mean life expectancy can only be appropriately calculated from mature KM data; and therefore, median survival is likely to be a more appropriate measure in this instance to inform life expectancy for end-of-life criteria.</p> <p>Overall, we are concerned that the recommendation may not fairly reflect the survival burden of patients who have been previously treated with ruxolitinib, have become relapsed/refractory or intolerant and are further along in their disease course</p> <p>Poor survival outcomes in current practice were observed in the global chart review outlined during Technical Engagement. Baseline characteristics have been provided in an appendix showing similarities to the JAKARTA-2 population.</p>
4	<p>For end-of-life criteria to be met, it is also required that fedratinib provide an expected extension to life of <math>\geq 3</math> months.</p> <p>The committee considered that fedratinib was likely to extend overall survival. However, it concluded that based on the evidence presented, the extent of this overall survival benefit was highly uncertain.</p> <p>JAKARTA-2 showed that the proportion of patients with spleen response was █████% (unadjusted data for intermediate-2 and high-risk patients), which was significantly higher than the SIMPLIFY-2 and PERSIST-2 BAT response in both the naïve comparison and in the indirect treatment comparisons. There is a wealth of published evidence investigating the relationship between survival and spleen size in myelofibrosis patients. 12 identified studies examining this relationship were presented in Appendix L.7. of the original submission. Of the 7 studies that investigated the relationship between change in spleen length, size or volume (with varying definitions of response threshold) and overall survival, all 7 found that spleen response was associated with positive survival outcomes in the investigative arm. 4 of the 7 studies presented hazard ratios to quantify the relationship:</p> <ul style="list-style-type: none"> <li>• Vannucchi et al. 2015 <sup>6</sup> - Evidence in the investigative arm supporting both spleen volume reduction (HR = 0.24) and spleen length reduction (HR = 0.28) having association with survival. Results not replicated in control arm (low number of responders)</li> <li>• Verstovsek et al. 2012 <sup>7</sup> - Patients who experienced a confirmed <math>\geq 50\%</math> reduction in palpable spleen size (n = 61) had significantly prolonged survival compared with the minority of patients (n = 23) with a &lt; 25% reduction in spleen from baseline (HR = 0.223; 95% CI, 0.097-0.512; P = .0001)</li> <li>• Mesa et al. 2016 <sup>8</sup> - Relative to patients who did not respond (&lt;10% SVR), those with a response (<math>\geq 35\%</math> SVR) had a hazard ratio of 0.294. Results not replicated in BAT arm (low number of responders)</li> </ul>



**Fedratinib for disease-related splenomegaly and symptoms in myelofibrosis [ID1501]**

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	<ul style="list-style-type: none"> <li>• Petti et al. 2002<sup>9</sup> - Response predictive of overall survival. In multivariate analysis, not achieving any type of response, either partial or complete, was associated with a HR of 3.9.</li> </ul> <p>This evidence is wholly supportive of a link between spleen response and survival benefit. Fedratinib has been shown to provide meaningful spleen response in a population relapsed, refractory or intolerant to ruxolitinib. Although there is uncertainty, the company have taken a conservative approach on estimating survival, which leads to an estimated survival that is greater than 3 months for fedratinib compared to BAT. Therefore, the company believe that both criteria for end-of-life would be met.</p>
5	<p>The company base case model assumed that people having fedratinib would discontinue after disease relapse.</p> <p>The committee felt that most people are likely to keep having fedratinib after losing disease response, although the proportion who will do so is uncertain.</p> <p>It was considered that the proportion of people who would continue treatment with fedratinib was uncertain and would likely be between the estimates of a company scenario (65%) and the ERG scenario (89%).</p> <p>In JAKARTA-2, prior to the clinical hold, 35% of patients had discontinued fedratinib. This would suggest that estimates of patients continuing long-term fedratinib greater than 65% would not be reasonable. The discontinuations comprised 18 patients (19%) due to AEs, six (6%) due to disease progression, three (3%) because of patient decision and seven (7%) for other reasons. The company expect that the proportion of patients who continue would only include those who initially responded to fedratinib. In revised cost-effectiveness analysis, it is assumed that 65% of responders continue fedratinib beyond the initial extrapolated time of discontinuation. This was supported with the clinicians surveyed by the company when asked this question.</p> <p>Early interim real-world data from the United States, where fedratinib has been licensed for treating myelofibrosis in patients who are JAKi naïve or have been previously treated with ruxolitinib since August 2019, indicates an observed discontinuation rate of █████ over the current study period. This does suggest the company assumptions is likely to be an overestimate for the continuation of fedratinib after a loss of response.</p> <p>One aspect the company did not explore was the dose of fedratinib when continued after loss of response. For ruxolitinib, lower doses are used in clinical practice, and therefore it would be expected that lower doses of fedratinib would also be used. The company did seek clinical advice and no dose was conclusively recommended as it was difficult to state without using fedratinib in this setting. The company are suggesting a lower dose intensity would be used in line with the current practice with ruxolitinib and have suggested a █████ RDI in a scenario analysis.</p>
6	<p>The company model has been described as having an overly complex model structure. There were also inconsistencies noted in modelling approach between treatment arms.</p> <p>Many of the challenges of the model structure relate to weaknesses in the dataset, that would only be overcome with more data collection, and that oversimplifying a challenging decision problem would have created separate issues.</p> <p>It was noted by the ERG that there were differences in the modelling between the treatment arms. The modelling approach between treatment arms differed partly due to data availability, and some differences were necessary to reflect how patients who receive fedratinib after</p>

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	<p>ruxolitinib undergo an altered treatment pathway to those who move onto best available therapy immediately.</p> <p>Some of the uncertainty and perceived complexity arises because of separating inputs for responders from non-responders – whereas in a simpler cohort model type, inputs would be pooled, and calculations would be based on the average patient. A pooled approach using pooled data that is available and can be conducted within the existing company model, which uses consistent curves between responders and non-responders, based on a dataset covering all JAKARTA-2 intermediate-2 and high-risk patients. In such an approach, the only significant difference to a typical cohort model is that a cohort model averages the patients at the beginning and uses the cohort inputs, whereas the DES model simulates each patient as an individual and averages the outcomes at the end. Such an analysis yields highly comparable ICERs to the company base case (within 2%), which supports the modelling assumptions that have been made in the submission.</p>
7	<p>The preferred ERG base case included settings that may not be representative of UK practice or population outcomes.</p> <p>During the TA386 process, wastage was included at the request of the ERG as they were concerned by the company assumption of no drug wastage. They noted that most adverse events are managed by dose reduction or interruption and that this would lead to additional costs. The experts during TA386 advised that assuming no drug wastage for ruxolitinib reflected its use in clinical practice. It is important to highlight that having access to the patient level data also supported the decision of no wastage. However, it is unclear whether this remains true as informal discussions with clinicians support the previous ERG assumption, which would require new packs or lead to use of multiple 5mg tablets. We therefore believe it is inappropriate to assume no ruxolitinib wastage in this submission.</p>

Insert extra rows as needed

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.

**Fedratinib for disease-related splenomegaly and symptoms in myelofibrosis [ID1501]**

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Comments received during our consultations 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.

1. Clinicaltrials.gov. An Efficacy and Safety Study of Fedratinib Compared to Best Available Therapy in Subjects With DIPSS-intermediate or High-risk Primary Myelofibrosis, Post-polycythemia Vera Myelofibrosis, or Post-essential Thrombocythemia Myelofibrosis and Previously Treated With Ruxolitinib (FREEDOM2). 2020. (Updated: 10 March 2020) Available at: <https://clinicaltrials.gov/ct2/show/NCT03952039>. Accessed: 13 March 2020.
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8. Mesa R, Miller CB, Thyne M, et al. Myeloproliferative neoplasms (MPNs) have a significant impact on patients' overall health and productivity: the MPN Landmark survey. *BMC cancer*. 2016; 16(1):167.
9. Petti MC, Latagliata R, Spadea T, et al. Melphalan treatment in patients with myelofibrosis with myeloid metaplasia. *Br J Haematol*. 2002; 116(3):576-81.

## Fedratinib for disease-related splenomegaly and symptoms in myelofibrosis [ID1501]

### Appendix

#### Scenario analysis results

The results of scenario analysis relevant to the ACD are presented in Table 1. The only scenarios included at Technical Engagement which produce higher ICERs than those listed below are the scenarios that assume only 44.9% ruxolitinib use within BAT.

**Table 1: ACD scenarios with new price discount**

Scenario	Incremental cost	Incremental QALYs	Incremental LYs	ICER per QALY	Difference to Base Case
ACD: Schain exponential OS distribution, equal % time in supportive care between arms	18,475	0.664	0.970	27,810	9,516
ACD: █% RDI for fedratinib in BAT	8,187	0.474	0.518	17,282	-1,012
ACD: Simplified pooled analysis (OS estimated from time 0 for both fedratinib and BAT)	8,191	0.440	0.544	18,609	-315
<b>Key:</b> ACD, appraisal consultation document; AML, acute myeloid leukaemia; BAT, best available therapy; ICER, incremental cost-effectiveness ratio; LYs, life years; OS, overall survival; QALYs, quality-adjusted life years. <b>Company base case ICER:</b> £18,294					

The economic model is shared with NICE and the ERG. For convenience, the inputs used to derive the scenarios are also listed in Table 2.

**Table 2: Inputs used to derive scenarios**

Scenario name	Excel named range	Scenario value
ACD: Schain exponential OS distribution, equal % time in supportive care between arms	schain_nr	Exponential
	schain_r	Exponential
	c_BAT_TTD_HR	1.16
ACD: █% RDI for fedratinib in BAT	c_fed_in_BAT_RDI	█%
ACD: Simplified pooled analysis (OS estimated from time 0 for both fedratinib and BAT)	c_OS_from_zero_text	Overall Survival From Model Entry
	c_source_OS_FED_NR	JAKARTA-2 (Pooled)
	c_source_OS_FED_R	JAKARTA-2 (Pooled)
	c_source_TTD_FED_NR	JAKARTA-2 (Pooled)
	c_source_TTD_FED_R	JAKARTA-2 (Pooled)
	OS_entry_cross_X	5
	c_Time_in_Care_NR	20%
c_Time_in_Care_R	20%	

## Fedratinib for disease-related splenomegaly and symptoms in myelofibrosis [ID1501]

### Chart review

Chart review data were summarised during Technical Engagement. Further details on patient characteristics have been summarised in Table 3. All patients had a risk status of intermediate-2 or higher at baseline. The patient characteristics for age, gender split and platelet count at baseline are comparable to those reported in the JAKARTA-2 study.

**Table 3: Chart review patient characteristics**

Characteristic	Chart review	JAKARTA-2 (Int2/HR)
Total patient number	████	████
Age (mean (SD))	██████████	██████████
Gender (n Male (%))	██████████	██████████
Platelet count at baseline (n (%))		
< 100 x 10 <sup>9</sup> /L	██████████	██████████
≥ 100 x 10 <sup>9</sup> /L	██████████	██████████
Unknown	██████████	██████████
<b>Key:</b> Int-2, intermediate-2; HR, high risk; n, number; SD, standard deviation.		

### Survey results

Results from the survey asking clinicians the estimated proportion of patients that would continue fedratinib after loss of response and dose likely to be used.

**Table 4: Use and dose of fedratinib after loss of response**

Consultant	% of pts likely to continue once response is lost	Dose of fedratinib
Clinician A	Approx. 66%	Dependant on blood counts - platelets
Clinician B	33%	Approx. 300-400mgs
Clinician C	65%	Unknown

**Fedratinib for disease-related splenomegaly and symptoms in myelofibrosis [ID1501]**

**US Real word fedratinib use**

The following data are interim data from various centres across the US where [redacted] patients have been initiated fedratinib after prior ruxolitinib treatment. Data on demographics, clinical characteristics and outcomes were collected retrospectively via electronic case report, which were completed by the treating clinician.

Inclusion criteria included:

- Patient diagnosed with primary myelofibrosis, post- essential thrombocythaemia myelofibrosis or post- polycythaemia vera myelofibrosis.
- Patient treated with fedratinib and initiated treatment on or after August 16, 2019 (granting of fedratinib license)
- Patient received prior treatment with ruxolitinib
- Patient completed a minimum of one cycle of fedratinib treatment

Exclusion criteria

- Past or current participant in any fedratinib-related clinical trial

Data generation is ongoing and follow up is currently less than 9 months.

**Table 4: Patient characteristics**

	<b>All Patients (n=[redacted])</b>	
<b>Age at initial MF diagnosis (years)</b>		
Mean, SD	[redacted]	[redacted]
Median, interquartile range	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
<b>Sex (n, %)</b>		
Female	[redacted]	[redacted]
Male	[redacted]	[redacted]
<b>Type of MF (n, %)</b>		
PMF	[redacted]	[redacted]
Post-PV MF	[redacted]	[redacted]
Post-ET MF	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
<b>Risk Score Present in Chart (n, %)</b>		
low	[redacted]	[redacted]
intermediate-1	[redacted]	[redacted]
intermediate-2	[redacted]	[redacted]
Intermediate undetermined	[redacted]	[redacted]
high risk	[redacted]	[redacted]
risk not assigned	[redacted]	[redacted]
<b>Discontinued FEDR (n, %) during Study Period</b>		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]

**Key:** ET MF, essential thrombocythaemia myelofibrosis; PMF, Primary myelofibrosis; PV MF, polycythaemia vera myelofibrosis; SD, standard deviation.

**Fedratinib for disease-related splenomegaly and symptoms in myelofibrosis [ID1501]**

**Table 5: Reason for fedratinib discontinuation**

Rationale for Discontinuation of fedratinib	Discontinued fedratinib (n= [REDACTED])	
Availability of alternative treatment options	[REDACTED]	[REDACTED]
Disease progression	[REDACTED]	[REDACTED]
Toxicity/intolerability	[REDACTED]	[REDACTED]
Patient choice	[REDACTED]	[REDACTED]
Persistent symptoms	[REDACTED]	[REDACTED]
Thrombocytopenia	[REDACTED]	[REDACTED]
Elevated white blood cell (WBC) count	[REDACTED]	[REDACTED]
Allogeneic stem-cell transplant	[REDACTED]	[REDACTED]
Other	[REDACTED]	[REDACTED]
<i>COVID infection</i>	[REDACTED]	[REDACTED]
<i>COVID pneumonia</i>	[REDACTED]	[REDACTED]
<i>Death</i>	[REDACTED]	[REDACTED]
<i>Sepsis</i>	[REDACTED]	[REDACTED]

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<p><b>Organisation name – Stakeholder or respondent</b> (if you are responding as an individual rather than a registered stakeholder please leave blank):</p>	<p><b>Leukaemia Care</b></p>
<p><b>Disclosure</b> Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.</p>	<p><b>None</b></p>
<p><b>Name of commentator person completing form:</b></p>	<p>[REDACTED]</p>
<p><b>Comment number</b></p>	<p style="text-align: center;"><b>Comments</b></p> <p style="text-align: center;">Insert each comment in a new row.</p>



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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that .....
1	We would like to reiterate the significant unmet need in this population. The group in whom ruxolitinib is no longer effective have a poor prognosis and most continue on an ineffective treatment or have only palliative care. As per our previous submissions, this treatment improves the quality of life for these patients as well as improving their survival.
2	Whilst we appreciate there are concerns about the clinical trial data, part of the reason that there is limited data on this treatment is due to the rarity of myelofibrosis. The STA process requires a body of evidence that is more difficult to collect in rare conditions, which is unfair for illnesses. This group of rare illnesses, yet not so rare as to qualify for HST, are unfairly disadvantaged by this process. Therefore, we feel the committee accept a higher degree of uncertainty than it is currently.
3	Trials are ongoing for this treatment, including the FREEDOM2 trial. Therefore, we ask that the committee consider this treatment for the Cancer Drugs Fund to resolve some of the uncertainties. The trial should not be dismissed due to the crossover in the FREEDOM2 trial, as this can be accounted for.

Insert extra rows as needed

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<p><b>Organisation name – Stakeholder or respondent</b> (if you are responding as an individual rather than a registered stakeholder please leave blank):</p>	<p><b>MPN Voice</b></p>
<p><b>Disclosure</b> Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.</p>	<p><b>None</b></p>
<p><b>Name of commentator person completing form:</b></p>	<p>[REDACTED]</p>
<p><b>Comment number</b></p>	<p style="text-align: center;"><b>Comments</b></p> <p style="text-align: center;">Insert each comment in a new row.</p>

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that .....
1	Patients for whom ruxolitinib fails or has failed to be effective have no other treatment options and their prognosis is very poor. Fedratinib has been demonstrated to be of value in terms of quality of life for these patients and it therefore meets a very significant unmet need owing to the complete lack of any other treatment options. We are concerned that the unique value that the drug represents to this patient group has been underestimated in the appraisal.
2	We are also concerned that the clinician experts' opinions regarding the survival benefits of fedratinib have not been properly understood, or accounted for, in the appraisal. The experts have pointed out that the proven benefit that the drug demonstrates in terms of symptom reduction, especially reduction of spleen size, is almost certainly reflected in extended survival of the patients in question. Admittedly, the trial data presented to date does not explicitly prove this, but the opinion of the world's leading MPN experts is clear in this respect and does not appear to have been properly acknowledged in the appraisal.
3	Myelofibrosis is, thankfully, a rare disease. Within the small number of MF patients, only an even smaller subset is in the category of 'post-ruxolitinib' treatment. It is therefore understandable that limited data is available for the type of full cost-benefit analysis that NICE would normally expect to perform. But the comparative lack of data is only due to the rarity of the disease and does not affect either (a) the effectiveness of the drug or (b) the unique benefit that it provides to patients for whom all other therapies have failed.  We believe, therefore, that 'post-rux' MF patients are being unfairly treated by this decision on the basis of the rarity of their situation.
4	We understand that further data regarding both the symptom reduction and the survival benefit of fedratinib will be published as part of the FREEDOM2 trial. We therefore urge the committee to revisit the appraisal at the earliest opportunity once the data has been published.
5	We understand that the pricing of the drug is an important factor in the committee's decision not to recommend fedratinib. However, in light of the concerns we have outlined above, we believe that there remains a strong argument for fedratinib to be made available to patients for whom no other effective treatment is available via the Cancer Drugs Fund. We therefore ask the committee to reconsider whether that option should be provided for these patients.
6	

Insert extra rows as needed

**Checklist for submitting comments**

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

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<p><b>Organisation name – Stakeholder or respondent</b> (if you are responding as an individual rather than a registered stakeholder please leave blank):</p>	
<p><b>Disclosure</b> Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.</p>	None
<p><b>Name of commentator person completing form:</b></p>	Claire Harrison

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Comment number	Comments
	<p>Insert each comment in a new row.</p> <p>Do not paste other tables into this table, because your comments could get lost – type directly into this table.</p>
Example 1	We are concerned that this recommendation may imply that .....
1	Patients for whom ruxolitinib fails or has failed to be effective have no other treatment options and their prognosis is very poor. The ERG and all experts agree this.
2	Fedratinib has been demonstrated to be of value in terms of quality of life for these patients and it therefore meets a very significant unmet need owing to the complete lack of any other treatment options. The issue of whether spleen response is linked to survival benefit was argued and disagreed with despite this being internationally accepted and accepted by other bodies eg FDA etc.
3	Given the above and the understanding that further data regarding both the spleen and symptom reduction and the survival benefit of fedratinib will be published as part of the FREEDOM 1 and 2 trials. May I respectfully ask why the drug has not been recommended to go to the CDF pending this and other real world data?
4	Can we please understand how it is in the UK patient best interest that they do not have access to this drug?

Insert extra rows as needed

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**Fedratinib for splenomegaly and symptoms in myelofibrosis.  
ERG Review of Company's Response to ACD**

Produced by School of Health and Related Research (ScHARR), The University of Sheffield

Authors Marrissa Martyn-St James, Research Fellow, ScHARR, University of Sheffield, Sheffield, UK  
Rachid Rafia, Senior Research Fellow, ScHARR, University of Sheffield, Sheffield, UK

Date of this document 30/07/2021

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## 1. Introduction

This short document summarises the company's response<sup>1</sup> to the appraisal consultation document (ACD)<sup>2</sup> and the ERG's review of the company's response.

This short document also summarises the revised company's base-case, as well as additional analyses conducted by the ERG following the ACD.

## 2. Summary of comments from the company and ERG's review

### 2.1. Uncertainties addressed by FREEDOM-2

The company notes that FREEDOM-2 and its inclusion in the cancer drug fund (CDF) would resolve some of the key uncertainties in modelling inputs, including survival benefit and that crossover design is a feature of many trials and health technology assessments.

As acknowledged in the company response,<sup>1</sup> the ERG notes the wording in the ACD document<sup>2</sup> that "*FREEDOM-2 may not robustly resolve the uncertainty around a fedratinib survival benefit because crossover is allowed at 6 months (or earlier with disease progression)*". The ERG agrees with the company that crossover is a feature of many trials and HTAs, but notes that it is difficult to assess the robustness of any crossover adjustment prior data being available. The ERG further notes that in TA386, while crossover from the control arms to ruxolitinib was allowed at 6 months in COMFORT-I (ruxolitinib vs. Placebo), crossover was allowed later, at 12 months in COMFORT-II (ruxolitinib vs. BAT).

The ERG further notes that while FREEDOM-2 is likely to address some of the uncertainties in the model, that some of the issues are likely to remain, particularly around the differences in assumptions of how long patients remain on fedratinib versus those who continue ruxolitinib (in the comparator arm). This could however be resolved using other means, such as agreeing a set of assumptions.

### 2.2. Life expectancy less than 24 month in the absence of fedratinib

The company makes a number of points to justify a life expectancy of less than 24 month in the absence of fedratinib:

1. The ERG notes that the values discussed at the committee meeting,<sup>2</sup> and used in the company's response<sup>1</sup> (Shain et al, 2019;<sup>3</sup> COMFORT-II), refer to patients who stop ruxolitinib. The ERG re-iterates that the company's analysis (population entering the economic model) assumes that 88.5% of patients continue on ruxolitinib in the comparator arm in line with SIMPLIFY-2 (that is also used for response rate), where the OS appears to be considerably better<sup>4, 5</sup> (albeit data

are only reliable for the first 24 weeks due to crossover beyond that point) compared with that reported in Schain et al (2019)<sup>3</sup> in people who stopped ruxolitinib.

2. The company suggests<sup>1</sup> that the use of the median survival (■■■■ months) is a more appropriate measure compared with the use of the mean value predicted in the economic model due to the tails in the KMs and extrapolation that is driven by censoring and low number of patients at risk. The company further suggests<sup>1</sup> that another clinically plausible extrapolation (the exponential) yields a mean survival of less than 24 months (■■■■ life years). The ERG notes that the company submission (CS)<sup>6</sup> included estimates from seven clinicians<sup>7</sup> (used in the CS<sup>6</sup> to select extrapolation choice) who were asked to provide estimates on the proportion on patients surviving at 1, 2, 5, 10, 15 and 20 years following treatment with fedratinib and BAT. As highlighted in the ERG report<sup>8</sup> (Section 4.3.4.6.5), this was not done using formal elicitation methods, and no attempt was made to quantify uncertainty in the experts' estimates and pooling of estimates across experts was done using simple averaging rather than behavioural aggregation. Despite these limitations, these estimates<sup>7</sup> provided in the CS<sup>6, 7</sup> can be used to assess whether the predictions using the Weibull distribution currently used in the model are optimistic. For transparency, the ERG compared the model predictions using the Weibull distribution (green dashed line) fitted to Schain (company's base-case) and the exponential distribution (blue dashed line) against the company's clinician consensus values for BAT<sup>7</sup> (orange cross) provided in the CS<sup>6, 7</sup> and included in the company's economic model (■■■■ 1). The ERG notes that the extrapolation using the Weibull distribution aligns well with the company's clinician consensus<sup>6, 7</sup> expectation in the long-term and therefore the model does not seem to produce an unrealistic tail. The curve also does not plateau as the extrapolation from fedratinib is used for BAT at the point of crossing (4.3 years). As highlighted in the ERG report,<sup>8</sup> the question asked was also unclear as experts were asked on the survival "post-ruxolitinib" and there was no mention that almost all patients are assumed to continue to receive ruxolitinib while achieving a suboptimal response for the comparator arm. It is therefore possible that these clinician consensus estimates may be pessimistic as there was no mention that the majority (88.5%) of patients in the comparator arm were assumed to be continued on ruxolitinib (that is the population entering the model).

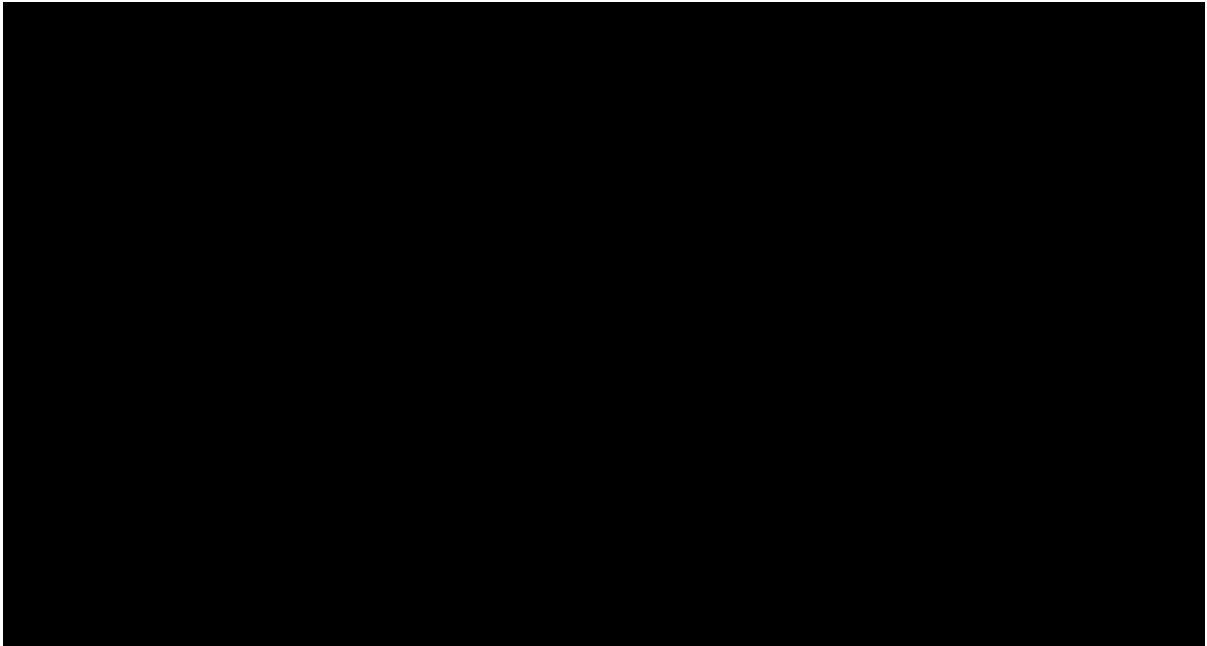
3. The company further justify the poor survival outcomes using data from a “global chart review” that was provided at technical engagement,<sup>9</sup> and provide in its response to ACD<sup>1</sup> baseline characteristics for age, gender and platelet counts only. The ERG was not able to assess the relevance of this study at technical engagement due to the lack of details (Issue 3 of ERG commentary on the company’s technical engagement response; p8-9<sup>10</sup>). For transparency, the company’s full description of the chart review is reproduced here as well the KMs in Figure 2 and **Figure 3**: *“The available survival data comprised intermediate-2 and high-risk patients who had experienced r/r/i to ruxolitinib and /or progression after ruxolitinib initiation and had either remained on ruxolitinib or discontinued. OS data was provided from the point of progression if it was available, or r/r/i if it was not. The outcomes of [REDACTED] patients were reported, [REDACTED] patients had a recorded progression event and [REDACTED] patients experienced a r/r/i event. Because the baseline for the time to OS event was taken from the point of progression if the data was available, only [REDACTED] of the patients had their baseline taken from the point of r/r/i”<sup>11</sup>.*

<sup>1 a</sup> Patients were considered to have progressed as defined and documented by the treating clinician.

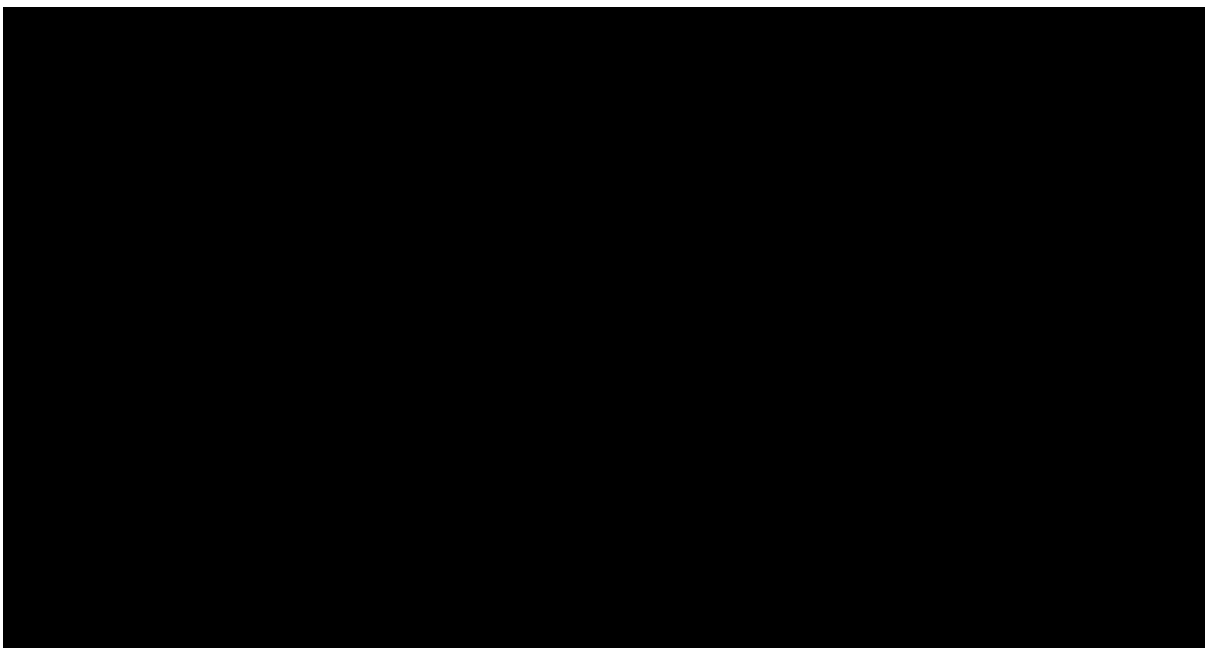
<sup>b</sup> Patients were considered to have relapsed if after ruxolitinib initiation and after 3 months of treatment with ruxolitinib, spleen size decreased and then subsequently increased (e.g., mild splenomegaly [at ruxolitinib initiation] to no splenomegaly to moderate splenomegaly); patients were considered to have refractory disease if after ruxolitinib initiation and after 3 months of treatment with ruxolitinib, spleen size increased without documentation of spleen size reduction (e.g., mild splenomegaly [at ruxolitinib initiation] to moderate splenomegaly); patients who continued to have severe splenomegaly throughout ruxolitinib treatment were considered to have refractory disease if treating physicians indicated the patient to have progressed while on treatment with ruxolitinib.

<sup>c</sup> Patients were defined intolerant to ruxolitinib if they were on ruxolitinib for  $\geq 28$  days, discontinued ruxolitinib within 90 days, and had an adverse event resulting in anemia, thrombocytopenia, or had a progressive disease with regard to anemia (including transformation to acute myeloid leukemia [AML]) as the reason for ruxolitinib discontinuation.

**Figure 2: Chart review: OS from point of progression or r/r/i of patients**



**Figure 3: Chart review: OS from patients where baseline == r/r/i**



Additional data provided in response to ACD<sup>1</sup> do not address the original concern from the ERG due to the lack of details preventing a full assessment of this study (Issue 3 of ERG commentary on the company's technical engagement response; p8-9<sup>10</sup>). In response to the ACD,<sup>1</sup> the company only provided the baseline characteristics for age, gender and platelet count

distribution and states that the patient characteristics at baseline are comparable to those reported in the JAKARTA-2 study, despite the ERG noting differences for 2 of the 3 baseline characteristics provided; gender (■■■■% vs ■■■■% male) and platelet count distribution (■■■■% [after removing unknown] vs. ■■■■% platelet count < 100 x 10<sup>9</sup>/L). As highlighted in the ERG's response to the technical engagement document,<sup>10</sup> it remains unclear whether patient characteristics are similar to the JAKARTA-2 trial in terms of proportion with high-risk MF, proportions that are relapsed/refractory and intolerant, MF subtype, transfusion dependence. It was also unclear to the ERG what the difference was between patients classified as progressed and those that are classified as r/t/i, and whether those that progressed have worse prognosis. The ERG further noted that there are significant limitations (biases) with comparing survival data from an observational study (the chart review) against OS from a clinical trial with strict inclusion criteria (JAKARTA-2). As highlighted in the ERG report,<sup>8</sup> to be recruited in JAKARTA-2, patients had to have a life expectancy of more than 6 months. The lack of details on the chart review makes it challenging to assess its relevance for survival.

### **2.3. Fedratinib is associated with a survival gain of more than 3 month**

The company indicates<sup>1</sup> that the proportion of patients with a spleen response was higher in JAKARTA-2 compared with that seen in the SIMPLIFY-2 trial<sup>4,5</sup> and that a number of studies are supportive of a relationship between spleen response and survival benefit.

The ERG notes that the difference in response rates is based on a comparison of JAKARTA-2 versus SIMPLIFY-2, with OS (first 6 month before cross-over) directly available in SIMPLIFY-2.<sup>4,5</sup> In a direct comparison between studies, fedratinib does not appear to be associated with a gain in survival at week 26 (until patients crossed over in SIMPLIFY-2) in both the unadjusted and adjusted analysis provided at technical engagement.<sup>9,10</sup>

While a survival gain cannot be ruled out as the follow-up is short, the large survival difference predicted in the company's model at week 26 does not align with the limited evidence available from SIMPLIFY-2<sup>4,5</sup> (that is also used for response rate and the proportion of patients on ruxolitinib). While it is possible that fedratinib could be associated with a survival gain, the extent of overall survival benefit is highly uncertain.

#### **2.4. Discontinuation of fedratinib after relapse**

The company argues<sup>1</sup> that patients would discontinue fedratinib based on evidence from JAKARTA-2 and supported by interim data from a real-world study in the US. The company states<sup>1</sup> that it “*expect that the proportion of patients who continue would only include those who initially responded to fedratinib. In revised cost-effectiveness analysis, it is assumed that 65% of responders continue fedratinib beyond the initial extrapolated time of discontinuation. This was supported with the clinicians surveyed by the company when asked this question*”.

The ERG re-iterates its concern that the issue relates to the modelling approach and the inconsistent assumptions used between treatment arms.<sup>8</sup> A key assumption in the company’s model is that patients in the comparator arm (BAT consisting mostly of ruxolitinib [88.5%]) remain on the same treatments [88.5% ruxolitinib] until reaching the supportive care health state. This is primarily justified in the CS<sup>6</sup> (CS, page 132, Section B.3.3.4.1) by the lack of alternative treatment options. This assumption therefore attempts to reflect UK clinical practice.

In contrast, in the company’s model, fedratinib is assumed to be given and stopped (as observed in JAKARTA-2) based on the time to discontinuation (TTD) curves from the trial (extrapolated time of discontinuation), with initial non-responders and 35% of initial responders subsequently receiving non-JAK BAT (consisting mostly hydroxyurea [HU]) for the remainder of their life until supportive care, and 65% of initial responders continuing to receive fedratinib (with 35% receiving non-BAT JAK) until reaching the supportive care health state in its revised base-case.

In other words, patients in the comparator arm (mostly ruxolitinib [88.5%]) cannot stop ruxolitinib (the proportion of ruxolitinib used is fixed throughout the model duration) until supportive care, while those on fedratinib are allowed to stop fedratinib before reaching the supportive care health state.

As ruxolitinib has a high drug acquisition cost, this issue/inconsistency becomes clearer in the scenarios where no survival difference is assumed. To illustrate this, in Table 1, the ERG present two analyses

- (a) the company’s base case (e.g a survival gain modelled using Schain and 65% of initial responders continue on fedratinib) and,
- (b) a scenario assuming equal OS and time on treatment (patients in the fedratinib and comparator arms have the same survival and time on treatment) – all other inputs are the same (e.g. 65% of initial responders on fedratinib remain on treatment).

Table 1: Comparison of results using the company’s base-case and a scenario assuming no OS difference and same time on treatment.

	Company’s base-case		Scenario assuming same OS and time on treatment	
	Comparator	Fedratinib	Comparator	Fedratinib
Drug acquisition costs	████████	████████	████████	████████
Other costs	████████	████████	████████	████████
<b>Total Cost</b>	████████	████████	████████	████████
<b>Total Lys</b>	████████	████████	████████	████████
<b>Total QALYs</b>	████████	████████	████████	████████
	ICER	£18,294	ICER	Dominant

**Abbreviations:** BAT: Best available therapy; FED: fedratinib, LY: life years; QALY: quality adjusted life years

When assuming the same OS and time on treatment curves (option included in the model), fedratinib becomes dominant because patients in the comparator arm (88.5% ruxolitinib) accrue more drug acquisition costs (████████) compared with those in the fedratinib arm (████████), this is despite the unit cost for fedratinib being higher than that of treatments in the comparator arm. As previously explained, this is because in the comparator arm, the proportion of ruxolitinib used is fixed at 88.5% throughout the model duration (until supportive care) while the proportion of patients continuing fedratinib is not (100% during the extrapolated TTD from JAKARTA-2 for both initial responders and non-responders; 0% beyond the extrapolated TTD for initial non-responders; and 65% beyond the extrapolated TTD for initial responders) until supportive care.

While the ERG does not question that patients may discontinue fedratinib at some point (due to adverse event or other reasons), the issue relates to the company’s modelling approach for the comparator arm that assume that patients on ruxolitinib (88.5% of the comparator arm) cannot stop treatment unless they reach supportive care.

### 2.5. Dose of fedratinib after loss of response.

In response to the ACD,<sup>1</sup> the company adds that “*One aspect the company did not explore was the dose of fedratinib when continued after loss of response. For ruxolitinib, lower doses are used in clinical practice, and therefore it would be expected that lower doses of fedratinib would also be used. The company did seek clinical advice and no dose was conclusively recommended as it was difficult to state without using fedratinib in this setting. The company are suggesting a lower dose intensity would be used in line with the current practice with ruxolitinib and have suggested a 75% RDI in a scenario analysis*”.



The ERG is not able to comment on the validity of this analysis, but notes that the value of 75% is arbitrary. The ERG further notes that in the company's model, the proportion of patients on low dose ruxolitinib (e.g 5mg) is based on the platelet count distribution to reflect the ruxolitinib marketing authorisation<sup>11</sup> (dosage based on platelet count distribution).

The SPC for ruxolitinib states: "*There is limited information to recommend a starting dose for patients with platelet counts between 50,000/mm<sup>3</sup> and <100,000/mm<sup>3</sup>. The maximum recommended starting dose in these patients is 5 mg twice daily and the patients should be titrated cautiously.*"

Low dose ruxolitinib for reasons other than platelet count < 100 x 10<sup>9</sup>/L is not considered in the company's model, and therefore equally, ruxolitinib costs could be lower than those in the company's model.

## **2.6. Complexity of the model**

The company justifies<sup>1</sup> its modelling approach by stating that "*many of the challenges of the model structure relate to weaknesses in the dataset, that would only be overcome with more data collection, and that oversimplifying a challenging decision problem would have created separate issues*" and that some of the complexities were caused by the decision to split patients by response status, but new analyses (not split by response status) yield similar results supporting its modelling assumptions.

The ERG wishes to highlight that its assessment of the complexity of the model is based on the information that is currently available to address the decision problem, rather than data that could become available in the future. The ERG further refers back to the ERG report<sup>8</sup> (Section 4.3.4.2) for a summary of issues that arose due to the complexity of the model.

## 2.7. Exclusion of wastage for ruxolitinib

The company argues<sup>1</sup> that wastage for ruxolitinib should be included and that “*it is important to highlight that having access to the patient level data also supported the decision of no wastage. However, it is unclear whether this remains true as informal discussions with clinicians support the previous ERG assumption, which would require new packs or lead to use of multiple 5mg tablets.*”

As highlighted in the ERG report,<sup>8</sup> this is not in line with the committee’s conclusion in TA386.<sup>12</sup> It is also possible that there could be less wastage in the relapse/refractory/intolerant (r/r/i) setting as more patients are likely to receive low dose ruxolitinib (5 mg) in the first place, although this remain unclear.

Additionally, as highlighted in the ERG report,<sup>8</sup> ruxolitinib costs are highly uncertain, and ruxolitinib costs may already have been overestimated as costs are calculated based on the platelet count distribution from JAKARTA-2. While the distribution of platelet count is not reported in SIMPLIFY-2, the mean platelet count was 126.5 (SD: 95.9) x 10<sup>9</sup>/L vs. [REDACTED] (SD: [REDACTED]) x 10<sup>9</sup>/L in JAKARTA-2.

New data provided by the company in response to ACD<sup>1</sup> indicates a higher proportion of patients with a platelet count < 100 x 10<sup>9</sup>/L ([REDACTED]% [after removing unknown]) compared with that in JAKARTA-2 ([REDACTED]) that is currently used in the model. This would therefore suggest that costs for ruxolitinib could be overestimated in the model.

The ERG further noted in its report<sup>8</sup> that the proportion of patients with a platelet count < 100 x 10<sup>9</sup>/L in other studies was 58% (median 91 x 10<sup>9</sup>/L) in Newberry et al (2017),<sup>13</sup> 45% in Kuykendall, 2017,<sup>14</sup> and 43.5% (mean 163.9 x 10<sup>9</sup>/L) in Palandri et al, 2019.<sup>15</sup>

### 3. Revised company’s base-case and ERG analyses following ACD

#### 3.1. Revised company’s base-case

The company amended its base-case (Table 2) assuming:

1. 65% of initial responders continue fedratinib with best available therapy,
  - a. 0% of non-responders continue fedratinib beyond trial TTD
2. Assuming the same rate of AML between treatment arms based on COMFORT-II,
3. An increase in the patient access scheme (PAS) in the form of a simple discount from [REDACTED] to [REDACTED].

Table 2: Company’s revised base-case

	BAT	FED
Total Costs	[REDACTED]	[REDACTED]
Total LYs	[REDACTED]	[REDACTED]
Total QALYs	[REDACTED]	[REDACTED]
	ICER	£18,294

**Abbreviations:** BAT: Best available therapy; FED: fedratinib, LY: life years; QALY: quality adjusted life years; RUX: ruxolitinib

#### 3.2. ERG’s analyses following ACD

For transparency and completeness, the ERG presents a number of analyses (combination of scenarios), assuming different proportions of patients that continue fedratinib (initial responders only, all patients) beyond the extrapolated trial TTD and different assumptions on survival benefit (difference in survival between arms based on a comparison of Schain vs. JAKARTA or no survival difference assumed based on SIMPLIFY-2 vs. JAKARTA-2).

Although this is open to debate, the ERG considers analysis 3 (Table 5) and 6 (Table 8) to be the most relevant due to the inconsistent approach between treatment arms, but present other analyses for transparency and completeness.

The ERG’s analyses include four additional amendments to the company revised base-case:

1. Exclusion of gender from the regression model when estimating utility values, as previously described in the ERG response addendum document,<sup>16</sup>
2. Assumption of a dose intensity of [REDACTED]% for patients continued on “suboptimal” fedratinib (instead of [REDACTED]% currently assumed), as previously described in the ERG response addendum document<sup>16</sup>

- as previously highlighted the value of [REDACTED]% is calculated by the company from the dose intensity in the subset of patients who did not get titrated (e.g patients who got up-titrated are removed altogether). The ERG noted that removing patients who got up-titrated (rather than capping the maximum dose to 400mg) is arbitrary and not appropriate. This is also not in line with the company's argument that the daily dose of fedratinib is 400 mg daily, and that that dose modifications are only referred in the SmPC in the context of managing treatment-emergent adverse reactions (see addendum clarification question C1<sup>17</sup>).
3. Use AE rates from the ITT population (rather than restricted to the intermediate-2/high risk population), as previously described in the ERG response addendum document,<sup>16</sup>
  4. Using the platelet count distribution from the chart review ([REDACTED]) provided by the company in its response to ACD,<sup>1</sup> instead of that of JAKARTA-2 ([REDACTED]) that is currently used in the model. The ERG expressed concern in the ERG report<sup>8</sup> that the mean platelet count in SIMPLIFY-2 was 126.5 (SD: 95.9) x 10<sup>9</sup>/L vs. [REDACTED] (SD: [REDACTED]) x 10<sup>9</sup>/L in JAKARTA-2, therefore potentially over-estimating the cost for ruxolitinib. The platelet count distribution from the chart review was not available to the ERG prior ACD, and therefore could not be assessed or included in previous analyses. As highlighted in Section 2.2 little detail is provided by the company but this study is used by the company to support poor survival outcomes for patients eligible for fedratinib. While the mean platelet count from the Chart review is not provided, the platelet count distribution (provided post-ACD<sup>1</sup>) is likely to resemble more that from SIMPLIFY-2 (used for response rate and proportion of patients on ruxolitinib) compared with the distribution from JAKARTA-2.

For transparency and completeness, and to account for the company assumptions,<sup>1</sup> analyses are presented including and excluding wastage for ruxolitinib. It should be noted that these analyses are conducted at list price for ruxolitinib, and therefore do not include the confidential PAS for ruxolitinib.

**3.2.1. Analyses assuming a survival difference (naïve comparison of OS from JAKARTA-2 and Schain et al, 2019 in patients who stop ruxolitinib)**

3.2.1.1. Analysis 1: Assume a fedratinib survival benefit and that 65% of **initial responders only** remain on fedratinib (this is similar to the company’s updated base case with the three amendments described above)

Table 3: Analysis 1

Wastage for RUX included			Wastage for RUX excluded		
	BAT	FED		BAT	FED
Total Cost	████████	████████	Total Cost	████████	████████
Total LYs	████████	████████	Total LYs	████████	████████
Total QALYs	████████	████████	Total QALYs	████████	████████
	ICER	£25,914		ICER	£30,063

**Abbreviations:** BAT: Best available therapy; FED: fedratinib, ICER: incremental cost-effectiveness ratio; LY: life years; QALY: quality adjusted life years; RUX: ruxolitinib

3.2.1.2. Analysis 2: Assume a fedratinib survival benefit and that 65% **of all patients** (initial responders and non-responders) remain on fedratinib

Table 4: Analysis 2

Wastage for RUX included			Wastage for RUX excluded		
	BAT	FED		BAT	FED
Total Cost	████████	████████	Total Cost	████████	████████
Total LYs	████████	████████	Total LYs	████████	████████
Total QALYs	████████	████████	Total QALYs	████████	████████
	ICER	£30,776		ICER	£34,925

**Abbreviations:** BAT: Best available therapy; FED: fedratinib, ICER: incremental cost-effectiveness ratio; LY: life years; QALY: quality adjusted life years; RUX: ruxolitinib

3.2.1.3. Analysis 3: Assume a fedratinib survival benefit and 88.5% of **all patients** (initial responders and non-responders) remain on fedratinib

Table 5: Analysis 3

Wastage for RUX included			Wastage for RUX excluded		
	BAT	FED		BAT	FED
Total Cost	████████	████████	Total Cost	████████	████████
Total LYs	████████	████████	Total LYs	████████	████████
Total QALYs	████████	████████	Total QALYs	████████	████████
	ICER	£35,965		ICER	£40,114

**Abbreviations:** BAT: Best available therapy; FED: fedratinib, ICER: incremental cost-effectiveness ratio; LY: life years; QALY: quality adjusted life years; RUX: ruxolitinib

### 3.2.2. Analyses assuming no survival difference

3.2.2.1. Analysis 4: Assume no fedratinib survival benefit and 65% of **initial responders only** remain on fedratinib

Table 6: Analysis 4

	Wastage for RUX included		Wastage for RUX excluded	
	BAT	FED	BAT	FED
Total Cost	██████	██████	██████	██████
Total LYs	██████	██████	██████	██████
Total QALYs	██████	██████	██████	██████
	ICER		ICER	
	Dominant		£3,414	

**Abbreviations:** BAT: Best available therapy; FED: fedratinib, ICER: incremental cost-effectiveness ratio; LY: life years; QALY: quality adjusted life years; RUX: ruxolitinib

3.2.2.2. Analysis 5: Assume no fedratinib survival benefit and 65% of **all patients** (initial responders and non-responders) remain on fedratinib

Table 7: Analysis 5

	Wastage for RUX included		Wastage for RUX excluded	
	BAT	FED	BAT	FED
Total Cost	██████	██████	██████	██████
Total LYs	██████	██████	██████	██████
Total QALYs	██████	██████	██████	██████
	ICER		ICER	
	£2,372		£22,915	

**Abbreviations:** BAT: Best available therapy; FED: fedratinib, ICER: incremental cost-effectiveness ratio; LY: life years; QALY: quality adjusted life years; RUX: ruxolitinib

3.2.2.3. Analysis 6: Assume no fedratinib survival benefit and 88.5% of **all patients** (initial responders and non-responders) remain on fedratinib

Table 8: Analysis 6

	Wastage for RUX included		Wastage for RUX excluded	
	BAT	FED	BAT	FED
Total Cost	██████	██████	██████	██████
Total LYs	██████	██████	██████	██████
Total QALYs	██████	██████	██████	██████
	ICER		ICER	
	£23,186		£43,729	

**Abbreviations:** BAT: Best available therapy; FED: fedratinib, ICER: incremental cost-effectiveness ratio; LY: life years; QALY: quality adjusted life years; RUX: ruxolitinib

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