NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

The following documents are made available to the consultees and commentators:

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

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Novartis
   - MPN Voice
   - Royal College of Pathologists
   - NHS England

   'No comment' response received from the Department of Health

3. **Comments on the Appraisal Consultation Document from experts:**
   - Mr C Clayton – patient expert, nominated by MPN Voice
   - Dr C Harrison – clinical expert, nominated by Royal College of Pathologists
   - Dr T Somervaille– clinical expert, nominated by Novartis Pharmaceuticals

4. **Comments on the Appraisal Consultation Document received through the NICE website**

5. **New evidence from Novartis**:
   - Updated patient access scheme submission
   - New evidence appendix

6. **Evidence Review Group review of new evidence**

7. **NICE request and company response - new analyses**

8. **Evidence Review Group review of subgroup analysis**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

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

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

Definitions:

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 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 determination (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, 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.

Comments received from consultees

Consultee	Comment [sic]	Response
Novartis	The manufacturer provided a submission in which the base case incremental cost-effectiveness ratio (ICER) for ruxolitinib including a patient access scheme (PAS) was £44,905 per quality-adjusted life years (QALY) gained. This was based on an analysis using data from the COMFORT-II trial which included a mixed population of patients with intermediate-2 and high risk myelofibrosis (MF). The Appraisal Committee (AC) concluded that (a) the most plausible ICER for patients with intermediate-2 or high risk MF was in the region of £45,000 per QALY gained and that (b) only high risk patients met all the end-of-life criteria and that additional weightings would apply to this population. As a result, the Committee's preliminary recommendation is that ruxolitinib is approved as an option for the treatment of patients with high risk MF providing the agreed PAS is in place. Patients with intermediate-2 MF also have a significant umet treatment need and the phase 3 studies have shown the benefit of ruxolitinib treatment in this sub-group both in terms of improvement in symptoms, quality of life and life expectancy. The evidence review group (ERG) identified minor programming errors and commented on the fact that some of the assumptions used in the original manufacturer's base case were conservative and likely to over-estimate the ICER. Consequently, in order to provide the most accurate estimate of the ICER, the base case presented by the manufacturer in the original submission to NICE (£44,905) has been revised to account for (a) errors identified by the ERG on the inclusion of leukaemic transformation (LT) in the economic model, (b) adjusting the baseline utility (c) change to the treatment pathways for responders to ruxolitinib and (d) the exclusion of lenolidomide. A revised PAS has also been offered by Novartis. These changes result in a revised base case ICER for ruxolitinib of £31,385 per QALY gained (including the revised PAS). The ICER is £31,240 per QALY gained in the probabilistic sensitivity analysis (with the revised PAS).	Comment noted. The Committee has considered the new evidence submitted after consultation on the appraisal consultation document (ACD) by the company and also the ERG's critique of the new evidence. For further information please see the relevant sections of the FAD (sections 3.40, 3.41, 3.42, 3.51-3.57 and sections 4.9, 4.11 and 4.12 of the FAD).

<table>
<tr><th>Consultee</th><th>Comment [sic]</th><th>Response</th></tr>
<tr><td></td><td>We believe that additional factors also need to be considered.
• Impact of MF on caregivers' quality of life. An exploratory analysis illustrates that, under a series of assumptions regarding the impact of MF on caregiver quality of life, the revised base case ICER (including PAS) can be reduced to £28,111 per QALY gained.
• Economic impact of MF on patients and carers. Various European studies have shown that MF can have a considerable economic impact on patients and their carers, both in terms of time devoted to caring by informal carers and loss of earnings for both patients and carers.
• Additional weighting due to end-of-life for the mixed population of patients with high and intermediate-2 risk MF. Data indicate the the survival of the combined group is in the region of 2 years from time of treatment initiation and therefore the full group could meet end-of-life criteria.
• Additional consideration when assessing the mixed population: consideration should be given to the fact that the Appraisal Committee has agreed that approximately half the population meets end-of-life criteria. As a result, the threshold against which cost-effectiveness for the whole group is assessed should be between £30,000 and £50,000.</td><td></td></tr>
<tr><td>Novartis</td><td>A small number of factual inaccuracies have been identified in the ACD, as outlined in Table 1 below.
Table 1 Factual inaccuracies
<table>
<tr><th>ACD document</th><th>Description of error</th><th>Description of amendment</th></tr>
<tr><td>Point 2.3
page 4</td><td>The cost of ruxolitinib is £3,600 for a 60-tablet pack of 15 mg or 20 mg tablets, or £1,800 for a 60-tablet pack of 5 mg tablets (excluding VAT; British National Formulary [BNF], edition 70). This corresponds to an annual cost of approximately £43,200 per patient (assuming a 15 mg or 20 mg dose, taken twice daily, 30 days per month).</td><td>The cost of ruxolitinib is £3,360 for a 56-tablet pack of 15 mg or 20 mg tablets, or £1,680 for a 56-tablet pack of 5 mg tablets (excluding VAT; British National Formulary [BNF], October 2015). This corresponds to an annual cost of approximately £43,680 per patient (assuming a 15 mg or 20 mg dose, taken twice daily for 52 weeks).</td></tr>
<tr><td>Point 3.14
page 9</td><td>Adverse event data were collected in COMFORT-I at 28 weeks and at 48 weeks in</td><td>Adverse event data were collected in COMFORT-I at 24 weeks and at 48 weeks in</td></tr>
</table></td><td>The FAD has been updated and the factual inaccuracies were corrected.
Please see sections 2.3, 3.14, 3.26, 3.28.</td></tr>
</table>

<table>
<tr><th>Consultee</th><th>Comment [sic]</th><th>Response</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>COMFORT-II.</td><td>COMFORT-II.</td></tr>
<tr><td>Point 3.26
page 15</td><td>Clinical effectiveness data used in the model was primarily obtained from the COMFORT-II trial, which enrolled intermediate-2 and high-risk patients whose disease did not respond to other therapies.</td><td>Clinical effectiveness data used in the model was primarily obtained from the COMFORT-II trial, which enrolled intermediate-2 and high-risk patients.
[NOTE: It was only the COMFORT-I study that enrolled patients whose disease did not respond to other therapies.]</td></tr>
<tr><td>Point 3.28
page 15/16</td><td>Dose intensity, duration, treatment or order of treatment were not recorded in the COMFORT-II trial.</td><td>Dose intensity, duration or order
of treatment were not recorded in the COMFORT-II trial.</td></tr>
</table>
</td><td></td></tr>
<tr><td>Novartis</td><td>Equality issues
Novartis believes that the preliminary recommendations could be regarded as discriminatory against patients with intermediate-2 risk MF. These patients have a similar burden of disease and unmet need to high risk patients as well as poor overall survival. The pivotal phase 3 COMFORT trials demonstrated the clinical benefit to be conferred on both intermediate-2 and high risk groups of patients and a large survival advantage and improvement in quality of life. A study using cluster analysis from prospectively gathered symptom burden data showed that the MF cluster with the highest symptom burden included high and intermediate-2 risk patients in exactly the same proportions (33.3%). Yet the preliminary recommendations would deny treatment to intermediate-2 risk patients.

In Scotland, ruxolitinib is approved for use in accordance with the licensed indication which is not specified by risk group. Approval in England and Wales of ruxolitinib in high risk patients only would result in inequality of access across the UK.

References were provided, but not replicated here.</td><td>Ruxolitinib is now recommended for the intermediate-2 risk subgroup as well as for the high-risk subgroup. Please see sections 4.12 and 4.16 of the FAD.</td></tr>
<tr><td>MPN Voice</td><td>Dear Committee C,</td><td>Comment noted. After consultation on the ACD, the</td></tr>
</table>

Consultee	Comment [sic]	Response
	I was very pleased to read your decision in the above consultation to approve Ruxolitinib for use for high risk MF patients. On behalf of the whole MPN community, thank you. We would, however, like to encourage the committee to reconsider its use for Intermediate 2 risk patients, for the following reasons: 1) IR-2 patients often have a very similar symptom burden to HR patients. Their symptoms are debilitating and totally life changing. Given the similarity of symptom burden, it seems unfair that they cannot access effective treatment. 2) On BAT, many IR-2 patients are not able to function at all. There is no effective BAT for them. Ruxolitinib has been shown to have an extraordinary effect on these patients, enabling them to return to their former lives. There is a fundamental unmet need for this patient group, and Ruxolitinib meets this need. 3) This decision is likely to place a huge psychological strain on us. Knowing that there is only one effective drug available to us, and that we need to progress to the worst stage of illness before we can access it will be intolerable for us. 4) Following from this, an unintended consequence of this decision is likely to be a serious cognitive dissonance: we don't want to deteriorate, of course, but patients may end up desiring a worsening of their condition so they can access a drug that will give them their life back. 5) We understand that the sooner patients start on Ruxolitinib, the greater efficacy the drug has on reduction of spleen size and overall symptoms. It seems like a sensible medical decision to avoid potential future complications, e.g. from an enlarged spleen, by treating early. 6) We feel the decision creates inequality amongst our patients. Both IR-2 and HR patients experience debilitating symptoms that prevent them from living a quality life, but only one group will have access to a transformative, innovative, step-change drug. 7) Similarly, given that IR-2 patients are likely to be younger, we feel that the decision discriminates against a certain age group. 8) We feel that the decision doesn't represent the best value for money for the British taxpayer. Ruxolitinib allows IR-2 patients and their carers to return to work, thus contributing to the economy through tax, productivity and consumer activity. 9) The pace of innovation in this field is rapid. Prolonged life for IR-2 may mean a more effective drug comes along in patients' lifetime. The hope that this gives is invaluable to us.	company requested permission which was granted by NICE, to present new evidence and a revised version of the model. The Committee considered the new evidence from the company on the cost-effectiveness of ruxolitinib in the intermediate-2 and high-risk subgroups, the Committee decided to recommend it also for the intermediate-2 risk subgroup of people with myelofibrosis. For further information see section 4.12 of the FAD.

Consultee	Comment [sic]	Response
	In the words of one IR-2 patient, "I couldn't imagine my life without it, I just wouldn't function at all. It kept me in one of the most demanding jobs for an extra 18 months." And in the words of another, "it would be very unfair for me to be able to take Rux through a trial, and for others to have to suffer without it." I do hope the above reasons give you ample motivation to reconsider approving the drug for Intermediate 2 patients. It's a decision that would send waves of relief and hope through our community. We would be grateful if you would reconsider.	
Royal College of Pathologists	The Royal College of Pathologists would like to thank you for the opportunity to comment on the Appraisal Consultation Document of this technology appraisal. The review undertaken by the appraisal committee has been fairly comprehensive as regards review of the available – and up to date- clinical data. However, the scale of the clinical benefits associated with ruxolitinib in Myelofibrosis (MF) has been under-appreciated. Both the COMFORT-I and II trials have been considered in detail – including the cross-over nature of these Phase III trials- and also data from the 4 non-randomised controlled studies of ruxolitinib in patients with Intermediate-1 risk MF or a low platelet count (ROBUST, JUMP, Study 258 and EXPAND). The committee have also considered the survival benefit associated with this agent. It is evident that ruxolitinib should not solely be reserved for those with high-risk disease. Real-world experience of this drug adds greatly to the evidence-base- treating expert clinicians have seen numerous patients with both Intermediate-II and High Risk disease demonstrate profound improvements in splenomegaly and problematic disease-related symptomatology when commenced on this agent. This translates to improved QOL. This is not the case with any of the other potential therapies that are currently available within the UK. This review does not substantially address the pertinent issue that the MF-related symptom burden is not directly linear with the IPSS or DIPSS score; therefore by excluding intermediate risk II patients there will often be inadequate management of symptomatology which can greatly impair QOL for these patients. It must also be recognised by the committee that the DIPSS is by nature dynamic and means the score obtained may be fluid. This under-appreciation of the potential clinical benefits will exclude many eligible patients. Approval of the drug for those only with HR disease and categorizing this as end of life style therapy is not entirely appropriate for this disorder. There are many patients who fall	Comment noted. After consultation on the ACD, the company requested permission which was granted by NICE, to present new evidence and a revised version of the model. The Committee considered the new evidence from the company on the cost-effectiveness of ruxolitinib in the intermediate-2 and high-risk subgroups, the Committee decided to recommend it also for the intermediate-2 risk subgroup of people with myelofibrosis. For further information see section 4.12 of the FAD.

Consultee	Comment [sic]	Response
	into lower risk IPSS/DIPSS categories and whom ruxoliutinib can offer profound improvements in objective symptom scores (as determined by the MPN-SAF) but also in splenomegaly and there is increasing evidence that it can confer a survival benefit. This is of particular importance for those individuals with MF who are not suitable for an allogeneic stem cell transplant due to age, co-morbidities or lack of a suitable stem cell source. It is noted that in one of the presented analyses ruxolitinib was associated with a 65% reduction in the risk of death compared with best available therapy in the RPSFT analysis (the corrected hazard ratio was confidential and therefore was not presented here). This potential survival benefit should not solely be considered for those with HR disease but also for those with Intermediate Risk disease. I note that the ERG was of the opinion that allo-HSCT should have been considered as BAT but this is not tenable – only a proportion of patients are suitable to move forward with this treatment option. Lastly, by excluding those with Intermediate-II risk disease for not meeting the end-of-life criterion of less than 24-months is not appropriate. Whilst appreciating the survival benefit suggested by the most recent data, using this criterion excludes the profound improvements in both splenomegaly and symptom burden that can be achieved by the use of this agent.	
NHS England	Has all of the relevant evidence been taken into account? Yes Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Yes they are reasonable interpretations of the evidence Are the provisional recommendations sound and a suitable basis for guidance to the NHS? No – section 1.1 is unclear in that it states that Ruxolitinib is recommended in certain situations in patients with myelofibrosis. It needs to make clear that this recommendation applies to patients with primary myelofibrosis or post polycythaemia myelofibrosis or post essential thrombocytosis myelofibrosis. Any other comments None	Comment noted. Section 1.1 of the FAD has been updated to reflect that ruxolitinib, is recommended for adults with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis, only in people with intermediate-2 or high-risk disease.

Comments received from clinical experts and patient experts

Nominating organisation	Comment [sic]	Response
Novartis	Given the terms of reference within which NICE operates, I concur that the relevant evidence seems to have been taken into account and that the summaries of clinical and cost effectiveness appear reasonable. That said, the decision not to extend funding of ruxolitinib to all myelofibrosis patients exhibiting clinical need is a concern. I urge the committee to reconsider its provisional recommendation to see if it can find some way, perhaps working with Novartis, to make this life changing drug available to the intermediate-2 population of patients as well as the high risk ones. There are many intermediate-2 patients who have intensely disabling symptoms (e.g. intractable itch, night sweats, weight loss) for whom this decision will deprive them of a remarkably effective treatment which transforms their lives. Further, the prolongation of life achieved with ruxolitinib appears superior for INT-2 patients in the COMFORT studies versus the high risk ones. It will be really tough watching and waiting for an INT-2 myelofibrosis patient to deteriorate into a high risk one before you can treat him/her with life prolonging, life changing treatment. Such treatment of course would have substantially improved their quality and quantity of life if introduced according to personalized clinical need rather than according to a rigid classification scoring system that neglects the needs of the individual. Of course, given that age>65 is one of the five contributing factors to the risk score in the IWG scoring system, NICE could be criticised here for ageism – a patient with the same set of symptoms and same clinical need age 60 will have to wait 5 years for treatment that would be directly and immediately available for a patient aged 66. If the committee is unable to alter its decision, it would be helpful to make an unequivocal statement in the text that the committee accepts that ruxolitinib is effective treatment for intermediate-2 patients, just that it was not deemed cost effective.	Comment noted. After consultation on the ACD, the company requested permission which was granted by NICE, to present new evidence and a revised version of the model. The Committee considered the new evidence from the company on the cost-effectiveness of ruxolitinib in the intermediate-2 and high-risk subgroups, the Committee decided to recommend it also for the intermediate-2 risk subgroup of people with myelofibrosis. For further information see section 4.12 of the FAD.
MPN Voice	Dear Sir, After reading the appraisal document for ruxolitinib I am concerned that it appears NICE is considering recommending it for patients with myelofibrosis who are classed as high risk only. I consider this to be a mis-placed assessment for the below reasons. As you may or may not remember I have attended both ruxolitinib appraisal in the role of an expert patient and it was only during the second one that I found out my own	Comment noted. After consultation on the ACD, the company requested permission which was granted by NICE, to present new evidence and a revised version of the model. The Committee considered the new evidence from the company on the cost-effectiveness of ruxolitinib in the intermediate-2 and high-risk subgroups, the Committee decided to recommend it also for the

Nominating organisation	Comment [sic]	Response
	classification. This is because I have MF after polycythaemia and when I found out too much about PV it resulted in me having a psychological breakdown. Thus I have found it better to restrict my knowledge of my disease. Ruxolitinib is recommended for the reduction of splenomegaly and disease related symptoms. Its EU drug licence makes no mention of what grade of MF is to be treated.To recommend ruxolitinib be used only in high grade patients implies that other grades do not have significant splenomegaly or disease related symptoms which is clearly wrong. I have intermediate 2 MF and at the first ruxolitinib appraisal remember that for the purposes of the economic assessment MF was considered to give the same level of fatigue as someone with metastatic breast cancer. Having worked as a GP and having MF myself I don't think that was an exaggeration as the fatigue is truly crippling. I have been taking ruxolitinib for 3 years and the results have been astonishing. When I first took it I was on the point of retiring as a full time GP. It meant I could continue in practice for a further 18 months doing one of the most strenuous jobs in the UK. If I were doing an easier job or was employed it is possible I would still be working and thus contributing to the national economy. I am fortunate to have been able to access this drug . I could not imagine being told that I would have to wait till I got worse if I found myself in those circumstances today. That would be intolerably cruel and place a huge negative psychological burden on someone who is already suffering a huge physical burden. NICE appears to have accepted that ruxolitinib both relieves the symptoms of MF and also extends the life of people with MF. I was told in a personal communication by [redacted] just before she presented such evidence to a European conference that ruxolitinib extends life. She elaborated that this reduced mortality was related both to the daily dose and the total lifetime dose. Thus to confine the use of ruxolitinib to high grade patients only is to reduce the influence it has on mortality as it would only be used in the group that has the highest mortality. Frankly that is perverse. It would mean the only treatment that carried any significant chance of extending	intermediate-2 risk subgroup of people with myelofibrosis. For further information see section 4.12 of the FAD. The Committee also considered that treatment with ruxolitinib provides an extension of life of more than an average of 3 months. Please see section 4.15 of the FAD.

Nominating organisation	Comment [sic]	Response
	useful life would be bone marrow transplant with all its attendant risks. Ruxolitinib is the only drug that improves both morbidity and mortality in people who have MF. It is also an orphan drug with all the economic implications that carries. I ask you to think again about recommending ruxolitinib only for people with high grade disease and to allow its use in a wider group of people. Thank you for taking the time to read this.	
Royal College of Physicians	Thank you for the opportunity to respond to this provisional ACD for Ruxolitinib for myelofibrosis. I find the outcome suggested extremely disappointing with regard to recommendation for high-risk patients, this is achieved by applying end of life rules and therefore would exclude many patients in need of ruxolitinib and for whom the committee decided there was robust evidence that this drug would significantly improve quality and duration of life. The extension of life was calculated at 24 months but has been calculated as longer in other studies. I have several comments: - Effectively this means since patients do die with intermediate 2 risk disease, without necessarily becoming high risk, that the ACD as it stands will deny these patients access to this drug. - My request is that the company is persuaded to apply a larger discount so that all patients within the scope of the phase 3 studies (COMFORT 1 and COMFORT-2) would then be eligible for treatment. - I have requested that my response is confidential as I am aware in my role as a disease expert that a lower discount may have been applied elsewhere in the EU. Thus I would urge the committee to consider any further price reductions offered by Novartis. - The decision as it stands also flouts, in addition to the phase 3 trials and the EMA approval, the strong personal evidence from [redacted] who was an	Comment noted. After consultation on the ACD, the company requested permission which was granted by NICE, to present new evidence and a revised version of the model. The Committee considered the new evidence from the company on the cost-effectiveness of ruxolitinib in the intermediate-2 and high-risk subgroups, the Committee decided to recommend it also for the intermediate-2 risk subgroup of people with myelofibrosis. For further information see section 4.12 of the FAD.

Nominating organisation	Comment [sic]	Response
	intermediate -2 risk patient of the life changing nature of his response to Ruxolitinib – he was able to work again. - The decision also means that there is be a disparity between NICE and the SMC for patients with this disease. - The risk stratification for MF varies newer molecular tests are being applied and integrated and other scoring systems such as DIPSS or DIPSS plus. Thus the distinction between IPSS Int-2 and high risk disease is very blurred with these other scoring systems. - The committee also heard about bone marrow transplant that more patients treated with Ruxolitinib would be able to receive this therapy for most transplants consideration would be given when the patient has intermediate risk-2 disease. - Access to newer therapies comes first via clinical trials. Decisions made by NICE strongly affect the access to UK patients for trials, many companies will reconsider allowing trials to run in the UK if patients are ultimately not able to access drugs. I am certain many of the arguments above are those which have been heard previously, I recognize the need for careful and evidence based approval of drugs through the NICE process and indeed have strong respect for it. I would however wish to repeat my urging of the committee to consider any further price reduction from Novartis before moving to a final decision.	

Comments received from commentators

Commentator	Comment [sic]	Response
ERG - NHS Centre for Reviews & Dissemination and Centre for Health Economics - York	We have spotted a few typographical errors in the ACD which are potentially misleading, listed below: Page 2 - date of 2nd Committee Meeting is wrong Page 5, third line from end - spelling of hydroxycarbamide Page 6, second line of section 3.5 - 'maintenance of reduction in spleen volume' Page 7, section 3.7 - replace 'portion' with 'proportion' (3 different places) Page 12, last word of section 3.19 - '100x109/L' Page 15, section 3.26 - COMFORT-II did not only enrol patients with disease that did not respond to other therapies Page 15, last line - I think 'duration, treatment' should read 'duration of treatment' Page 16, section 3.31 - the sentence beginning four lines from the bottom of the page is unclear, suggest changing to read “After the initial treatment phase, patients starting on ruxolitinib faced a different mortality rate according to whether they responded to treatment in the initial phase, did not respond to treatment in the initial phase or stopped treatment in the initial phase.” Page 39, first line - '(RCT)' should read '(non-RCTs)' Page 39, second line 'intermediate-risk' should read 'intermediate-1 risk' Page 40, third line 'active treatment group' should read 'active treatment comparator group'	Comments noted. The FAD has been updated and the factual inaccuracies were corrected. Please see sections 3.3, 3.5, 3.7, 3.19, 3.26, 3.28, 3.31, and the table summarising the Appraisal Committee’s key conclusions.

Summary of comments received from members of the public

Theme	Response
Ruxolitinib should be recommended for intermediate-risk myelofibrosis and to all type of myelofibrosis.	Comment noted. After consultation on the ACD, the company requested permission which was granted by NICE, to present new evidence and a revised version of the model. The Committee considered the new evidence from the company on the cost-effectiveness of ruxolitinib in the intermediate-2 and high-risk subgroups, the Committee decided to recommend it also for the intermediate-2 risk subgroup of people with myelofibrosis. For further information see section 4.12 of the FAD. Section 1.1 of the FAD has been updated to reflect that ruxolitinib, is recommended for adults with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis, only in people with intermediate 2 or high-risk disease.
Ruxolitinib improves patient's wellbeing and quality of life, enables them to live a more active life and return to work. Ruxolitinib also improves the symptoms of myelofibrosis and decreases the size of the spleen.	Comment noted. The Committee discussed the impact of disease-related splenomegaly or symptoms of myelofibrosis and concluded that improving the symptoms would be greatly beneficial to the wellbeing of people with myelofibrosis and their families. For further information, please see section 4.1 of the FAD.
Ruxolitinib gives hope to people with myelofibrosis, both primary and secondary, and to their carers.	Comment noted. The Committee considered the impact of myelofibrosis on the quality of life of patients and their families. It concluded that improving symptoms associated with myelofibrosis would be greatly beneficial. The Committee also considered the new evidence submitted by the company at ACD stage, which took into account the impact of ruxolitinib on the quality of life of carers of people with myelofibrosis. It agreed that carers' health and quality of life can be affected by caring, but did not consider the results robust and also did not consider that myelofibrosis stood out amongst severe illnesses in having a more profound carer burden. For further information please see sections 4.1 and 4.11 of the FAD.

National Institute for Health and Care Excellence

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

RESPONSE TO APPRAISAL CONSULTATION DOCUMENT
10 November 2015

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1 Summary

The manufacturer provided a submission in which the base case incremental cost-effectiveness ratio (ICER) for ruxolitinib including a patient access scheme (PAS) was £44,905 per quality-adjusted life years (QALY) gained. This was based on an analysis using data from the COMFORT-II trial which included a mixed population of patients with intermediate-2 and high risk myelofibrosis (MF). The Appraisal Committee (AC) concluded that (a) the most plausible ICER for patients with intermediate-2 or high risk MF was in the region of £45,000 per QALY gained and that (b) only high risk patients met all the end-of-life criteria and that additional weightings would apply to this population.

As a result, the Committee's preliminary recommendation is that ruxolitinib is approved as an option for the treatment of patients with high risk MF providing the agreed PAS is in place.

Patients with intermediate-2 MF also have a significant umet treatment need and the phase 3 studies have shown the benefit of ruxolitinib treatment in this sub-group both in terms of improvement in symptoms, quality of life and life expectancy.

The evidence review group (ERG) identified minor programming errors and commented on the fact that some of the assumptions used in the original manufacturer's base case were conservative and likely to over-estimate the ICER.

Consequently, in order to provide the most accurate estimate of the ICER, the base case presented by the manufacturer in the original submission to NICE (£44,905) has been revised to account for (a) errors identified by the ERG on the inclusion of leukaemic transformation (LT) in the economic model, (b) adjusting the baseline utility (c) change to the treatment pathways for responders to ruxolitinib and (d) the exclusion of lenolidomide.

A revised PAS has also been offered by Novartis.

These changes result in a revised base case ICER for ruxolitinib of £31,385 per QALY gained (including the revised PAS). The ICER is £31,240 per QALY gained in the probabilistic sensitivity analysis (with the revised PAS).

We believe that additional factors also need to be considered.

- **Impact of MF on caregivers' quality of life**. An exploratory analysis illustrates that, under a series of assumptions regarding the impact of MF on caregiver quality of life, the revised base case ICER (including PAS) can be reduced to £28,111 per QALY gained.
- **Economic impact of MF on patients and carers**. Various European studies have shown that MF can have a considerable economic impact on patients and their carers,

both in terms of time devoted to caring by informal carers and loss of earnings for both patients and carers.

- **Additional weighting due to end-of-life for the mixed population of patients with high and intermediate-2 risk MF**. Data indicate the the survival of the combined group is in the region of 2 years from time of treatment initiation and therefore the full group could meet end-of-life criteria.

- **Additional consideration when assessing the mixed population**: consideration should be given to the fact that the Appraisal Committee has agreed that approximately half the population meets end-of-life criteria. As a result, the threshold against which cost-effectiveness for the whole group is assessed should be between £30,000 and £50,000.

2 Factual inaccuracies

A small number of factual inaccuracies have been identified in the ACD, as outlined in Table 1 below.

Table 1 Factual inaccuracies

ACD document	Description of error	Description of amendment
Point 2.3 page 4	The cost of ruxolitinib is £3,600 for a 60-tablet pack of 15 mg or 20 mg tablets, or £1,800 for a 60-tablet pack of 5 mg tablets (excluding VAT; British National Formulary [BNF], edition 70). This corresponds to an annual cost of approximately £43,200 per patient (assuming a 15 mg or 20 mg dose, taken twice daily, 30 days per month).	The cost of ruxolitinib is £3,360 for a 56-tablet pack of 15 mg or 20 mg tablets, or £1,680 for a 56-tablet pack of 5 mg tablets (excluding VAT; British National Formulary [BNF], October 2015). This corresponds to an annual cost of approximately £43,680 per patient (assuming a 15 mg or 20 mg dose, taken twice daily for 52 weeks).
Point 3.14 page 9	Adverse event data were collected in COMFORT-I at 28 weeks and at 48 weeks in COMFORT-II.	Adverse event data were collected in COMFORT-I at 24 weeks and at 48 weeks in COMFORT-II.
Point 3.26 page 15	Clinical effectiveness data used in the model was primarily obtained from the COMFORT-II trial, which enrolled intermediate-2 and high-risk patients whose disease did	Clinical effectiveness data used in the model was primarily obtained from the COMFORT-II trial, which enrolled intermediate-2 and high-risk

	not respond to other therapies.	patients. [NOTE: It was only the COMFORT-I study that enrolled patients whose disease did not respond to other therapies.]
Point 3.28 page 15/16	Dose intensity, duration, treatment or order of treatment were not recorded in the COMFORT-II trial.	Dose intensity, duration or order of treatment were not recorded in the COMFORT-II trial.

3 Equality issues

Novartis believes that the preliminary recommendations could be regarded as discriminatory against patients with intermediate-2 risk MF. These patients have a similar burden of disease and unmet need to high risk patients as well as poor overall survival. The pivotal phase 3 COMFORT trials demonstrated the clinical benefit to be conferred on both intermediate-2 and high risk groups of patients and a large survival advantage and improvement in quality of life. A study using cluster analysis from prospectively gathered symptom burden data showed that the MF cluster with the highest symptom burden included high and intermediate-2 risk patients in exactly the same proportions (33.3%).[1,2] Yet the preliminary recommendations would deny treatment to intermediate-2 risk patients.

In Scotland, ruxolitinib is approved for use in accordance with the licensed indication which is not specified by risk group. Approval in England and Wales of ruxolitinib in high risk patients only would result in inequality of access across the UK.

References

1 Geyer HL SR, Dueck AC et al. Distinct clustering of symptomatic burden among myeloproliferative neoplasm patients: retrospective assessment in 1470 patients. *Blood* 2014; **123**: 3803-10.

2 Geyer HL SR, Dueck AC et al. Distinct clustering of symptomatic burden among myeloproliferative neoplasm patients: retrospective assessment in 1470 patients. *Blood* 2014; **123**: Appendix.

Received by email:

Dear Committee C,

I was very pleased to read your decision in the above consultation to approve Ruxolitinib for use for high risk MF patients. On behalf of the whole MPN community, thank you.

We would, however, like to encourage the committee to reconsider its use for Intermediate 2 risk patients, for the following reasons:

1) IR-2 patients often have a very similar symptom burden to HR patients. Their symptoms are debilitating and totally life changing. Given the similarity of symptom burden, it seems unfair that they cannot access effective treatment.

2) On BAT, many IR-2 patients are not able to function at all. There is no effective BAT for them. Ruxolitinib has been shown to have an extraordinary effect on these patients, enabling them to return to their former lives. There is a fundamental unmet need for this patient group, and Ruxolitinib meets this need.

3) This decision is likely to place a huge psychological strain on us. Knowing that there is only one effective drug available to us, and that we need to progress to the worst stage of illness before we can access it will be intolerable for us.

4) Following from this, an unintended consequence of this decision is likely to be a serious cognitive dissonance: we don't want to deteriorate, of course, but patients may end up desiring a worsening of their condition so they can access a drug that will give them their life back.

5) We understand that the sooner patients start on Ruxolitinib, the greater efficacy the drug has on reduction of spleen size and overall symptoms. It seems like a sensible medical decision to avoid potential future complications, e.g. from an enlarged spleen, by treating early.

6) We feel the decision creates inequality amongst our patients. Both IR-2 and HR patients experience debilitating symptoms that prevent them from living a quality life, but only one group will have access to a transformative, innovative, step-change drug.

7) Similarly, given that IR-2 patients are likely to be younger, we feel that the decision discriminates against a certain age group.

8) We feel that the decision doesn't represent the best value for money for the British taxpayer. Ruxolitinib allows IR-2 patients and their carers to return to work, thus contributing to the economy through tax, productivity and consumer activity.

9) The pace of innovation in this field is rapid. Prolonged life for IR-2 may mean a more effective drug comes along in patients' lifetime. The hope that this gives is invaluable to us.

In the words of one IR-2 patient, "I couldn't imagine my life without it, I just wouldn't function at all. It kept me in one of the most demanding jobs for an extra 18 months."

And in the words of another, "it would be very unfair for me to be able to take Rux through a trial, and for others to have to suffer without it."

I do hope the above reasons give you ample motivation to reconsider approving the drug for Intermediate 2 patients. It's a decision that would send waves of relief and hope through our community.

We would be grateful if you would reconsider.

Many thanks

[redacted]

MPN Voice

The Royal College of Pathologists
Pathology: the science behind the cure

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

The Royal College of Pathologists would like to thank you for the opportunity to comment on the Appraisal Consultation Document of this technology appraisal.

The review undertaken by the appraisal committee has been fairly comprehensive as regards review of the available – and up to date- clinical data. However, the scale of the clinical benefits associated with ruxolitinib in Myelofibrosis (MF) has been under-appreciated.

Both the COMFORT-I and II trials have been considered in detail – including the cross-over nature of these Phase III trials- and also data from the 4 non-randomised controlled studies of ruxolitinib in patients with Intermediate-1 risk MF or a low platelet count (ROBUST, JUMP, Study 258 and EXPAND). The committee have also considered the survival benefit associated with this agent.

It is evident that ruxolitinib should not solely be reserved for those with high-risk disease. Real-world experience of this drug adds greatly to the evidence-base- treating expert clinicians have seen numerous patients with both Intermediate-II and High Risk disease demonstrate profound improvements in splenomegaly and problematic disease-related symptomatology when commenced on this agent. This translates to improved QOL. This is not the case with any of the other potential therapies that are currently available within the UK. This review does not substantially address the pertinent issue that the MF-related symptom burden is not directly linear with the IPSS or DIPSS score; therefore by excluding intermediate risk II patients there will often be inadequate management of symptomatology which can greatly impair QOL for these patients. It must also be recognised by the committee that the DIPSS is by nature dynamic and means the score obtained may be fluid. This under-appreciation of the potential clinical benefits will exclude many eligible patients.

Approval of the drug for those only with HR disease and categorizing this as end of life style therapy is not entirely appropriate for this disorder. There are many patients who fall into lower risk IPSS/DIPSS categories and whom ruxoliutinib can offer profound improvements in objective symptom scores (as determined by the MPN-SAF) but also in splenomegaly and there is increasing evidence that it can confer a survival benefit. This is of particular importance for those individuals with MF who are not suitable for an allogeneic stem cell transplant due to age, co-morbidities or lack of a suitable stem cell source. It is noted that in one of the presented analyses ruxolitinib was associated with a 65% reduction in the risk of death compared with best available therapy in the RPSFT analysis (the corrected hazard ratio was confidential and therefore was not presented here). This potential survival benefit should not solely be considered for those with HR disease but also for those with Intermediate Risk disease. I note that the ERG was of the opinion that allo-HSCT should have been considered as BAT but this is not tenable – only a proportion of patients are suitable to move forward with this treatment option.

Lastly, by excluding those with Intermediate-II risk disease for not meeting the end-of-life criterion of less than 24-months is not appropriate. Whilst appreciating the survival benefit suggested by the most recent data, using this criterion excludes the profound improvements in both splenomegaly and symptom burden that can be achieved by the use of this agent.

NHS England Response to NICE ACD – Ruxolitinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis (review of TA289)

Please find NHS England's response to the ACD – Ruxolitinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis which has been reviewed by the Chemotherapy CRG

Has all of the relevant evidence been taken into account?
Yes
Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
Yes they are reasonable interpretations of the evidence
Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
No – section 1.1 is unclear in that it states that Ruxolitinib is recommended in certain situations in patients with myelofibrosis. It needs to make clear that this recommendation applies to patients with primary myelofibrosis or post polycythaemia myelofibrosis or post essential thrombocytosis myelofibrosis.
Any other comments
None

Contact details

Title (e.g. Dr, Mr, Ms, Prof)	[redacted]
Name	[redacted]
Job title or role	[redacted]
Email address	[redacted]

Received by email:

Dear Sir,

After reading the appraisal document for ruxolitinib I am concerned that it appears NICE is considering recommending it for patients with myelofibrosis who are classed as high risk only. I consider this to be a mis-placed assessment for the below reasons. As you may or may not remember I have attended both ruxolitinib appraisal in the role of an expert patient and it was only during the second one that I found out my own classification. This is because I have MF after polycythaemia and when I found out too much about PV it resulted in me having a psychological breakdown. Thus I have found it better to restrict my knowledge of my disease.

Ruxolitinib is recommended for the reduction of splenomegaly and disease related symptoms. Its EU drug licence makes no mention of what grade of MF is to be treated.To recommend ruxolitinib be used only in high grade patients implies that other grades do not have significant splenomegaly or disease related symptoms which is clearly wrong.

I have intermediate 2 MF and at the first ruxolitinib appraisal remember that for the purposes of the economic assessment MF was considered to give the same level of fatigue as someone with metastatic breast cancer. Having worked as a GP and having MF myself I don't think that was an exaggeration as the fatigue is truly crippling.

I have been taking ruxolitinib for 3 years and the results have been astonishing. When I first took it I was on the point of retiring as a full time GP. It meant I could continue in practice for a further 18 months doing one of the most strenuous jobs in the UK. If I were doing an easier job or was employed it is possible I would still be working and thus contributing to the national economy.

I am fortunate to have been able to access this drug. I could not imagine being told that I would have to wait till I got worse if I found myself in those circumstances today. That would be intolerably cruel and place a huge negative psychological burden on someone who is already suffering a huge physical burden.

NICE appears to have accepted that ruxolitinib both relieves the symptoms of MF and also extends the life of people with MF. I was told in a personal communication by [redacted] just before she presented such evidence to a European conference that ruxolitinib extends life. She elaborated that this reduced mortality was related both to the daily dose and the total lifetime dose. Thus to confine the use of ruxolitinib to high grade patients only is to reduce the influence it

has on mortality as it would only be used in the group that has the highest mortality. Frankly that is perverse.

It would mean the only treatment that carried any significant chance of extending useful life would be bone marrow transplant with all its attendant risks.

Ruxolitinib is the only drug that improves both morbidity and mortality in people who have MF. It is also an orphan drug with all the economic implications that carries.

I ask you to think again about recommending ruxolitinib only for people with high grade disease and to allow its use in a wider group of people.

Thank you for taking the time to read this.

Yours sincerely

Colin Clayton

Response on behalf of Professor Claire Harrison representing RCP.

Thank you for the opportunity to respond to this provisional ACD for Ruxolitinib for myelofibrosis.

I find the outcome suggested extremely disappointing with regard to recommendation for high-risk patients, this is achieved by applying end of life rules and therefore would exclude many patients in need of ruxolitinib and for whom the committee decided there was robust evidence that this drug would significantly improve quality and duration of life. The extension of life was calculated at 24 months but has been calculated as longer in other studies.

I have several comments:

- Effectively this means since patients do die with intermediate 2 risk disease, without necessarily becoming high risk, that the ACD as it stands will deny these patients access to this drug.
- My request is that the company is persuaded to apply a larger discount so that all patients within the scope of the phase 3 studies (COMFORT 1 and COMFORT-2) would then be eligible for treatment.
- I have requested that my response is confidential as I am aware in my role as a disease expert that a lower discount may have been applied elsewhere in the EU. Thus I would urge the committee to consider any further price reductions offered by Novartis.

- The decision as it stands also flouts, in addition to the phase 3 trials and the EMA approval, the strong personal evidence from [redacted] who was an intermediate -2 risk patient of the life changing nature of his response to Ruxolitinib – he was able to work again.

- The decision also means that there is be a disparity between NICE and the SMC for patients with this disease.

- The risk stratification for MF varies newer molecular tests are being applied and integrated and other scoring systems such as DIPSS or DIPSS plus. Thus the distinction between IPSS Int-2 and high risk disease is very blurred with these other scoring systems.

- The committee also heard about bone marrow transplant that more patients treated with Ruxolitinib would be able to receive this therapy for most transplants consideration would be given when the patient has intermediate risk-2 disease.

- Access to newer therapies comes first via clinical trials. Decisions made by NICE strongly affect the access to UK patients for trials, many companies will reconsider allowing trials to run in the UK if patients are ultimately not able to access drugs.

I am certain many of the arguments above are those which have been heard previously, I recognize the need for careful and evidence based approval of drugs through the NICE process and indeed have strong respect for it. I would however wish to repeat my urging of the committee to consider any further price reduction from Novartis before moving to a final decision.

Given the terms of reference within which NICE operates, I concur that the relevant evidence seems to have been taken into account and that the summaries of clinical and cost effectiveness appear reasonable.

That said, the decision not to extend funding of ruxolitinib to all myelofibrosis patients exhibiting clinical need is a concern. I urge the committee to reconsider its provisional recommendation to see if it can find some way, perhaps working with Novartis, to make this life changing drug available to the intermediate-2 population of patients as well as the high risk ones.

There are many intermediate-2 patients who have intensely disabling symptoms (e.g. intractable itch, night sweats, weight loss) for whom this decision will deprive them of a remarkably effective treatment which transforms their lives. Further, the prolongation of life achieved with ruxolitinib appears superior for INT-2 patients in the COMFORT studies versus the high risk ones.

It will be really tough watching and waiting for an INT-2 myelofibrosis patient to deteriorate into a high risk one before you can treat him/her with life prolonging, life changing treatment. Such treatment of course would have substantially improved their quality and quantity of life if introduced according to personalized clinical need rather than according to a rigid classification scoring system that neglects the needs of the individual.

Of course, given that age>65 is one of the five contributing factors to the risk score in the IWG scoring system, NICE could be criticised here for ageism – a patient with the same set of symptoms and same clinical need age 60 will have to wait 5 years for treatment that would be directly and immediately available for a patient aged 66.

If the committee is unable to alter its decision, it would be helpful to make an unequivocal statement in the text that the committee accepts that ruxolitinib is effective treatment for intermediate-2 patients, just that it was not deemed cost effective.

Tim Somervaille

10 November 2015

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD: I have been taking ruxolitinib for myelofibrosis since diagnosis two and a half years ago. I was probably classified as medium risk on diagnosis. It has transformed my life: controlled my symptoms, enabled me to live a useful and productive life, and I now understand given me the possibility of extra years of life which I expect to enjoy. PLEASE don't restrict this marvellous drug to high risk patients.	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD: I suffer form Polycytheamia Vera and I am therefore at risk of developing post polycythaemia vera myelofibrosis. I am concerned that the recommendation is for use in high risk patients only as I understand that the drug has been shown to relieve symptoms AND extend life expectancy for all of those suffering from myelofibrosis. I believe that the extended life expectancy justifies the cost of treatment.	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3	

(The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	Patient with Post Polycythemia Myleofibrosis

Comments on individual sections of the ACD:

As a 60 year old patient recently diagnosed with post Poycythemia Myleofibrosis I am concerned that availability of ruxolitinib may be restricted to a limited number of High risk patients only. Despite my condition I continue to work full time and do not claim any Government benefits, I have a significantly enlarged Spleen (17cm) and my Consultant has just raised the possibility of my medication being changed from Hydroxycarbamide to ruxolitinib that will significantly reduce the many symptoms I am suffering as well as potentially extending my life. I do hope that the final recommendation on the availability of this drug will make it available to all Myleofibrosis patients.

Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No

Notes	
Comments on individual sections of the ACD: my concern is that at present it seems ruxolitinib may only be approved for high risk patients. I have concerns about this, since the approved indication is for spleen reduction and symptoms regardless of disease stage. I believe clinical trials have shown that patients with intermediate risk disease benefit in these aspects but also more importantly may gain years of life with this drug.	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD: I have polycythemia - an MPN. The next step along the way for me may well be an enlarged spleen and myelofibrosis. Research and clinical trials have shown that Ruxolitinib can be wholly effective in NONE high risk patients in reducing spleen size and enhancing quality of life for MPN patients. PLEASE do not put cost before treatment. I have no doubt that you, who are reading this, are in good health. Only when your health fails do you realise the importance of effective medication at all stages. I wish you the best of health for your lifetime, but please consider those of us who may not be so fortunate. MPN's have massive effects on both quality and indeed length of life.	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the	

evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	

Comments on individual sections of the ACD:

I am a patient diagnosed with an MPN and having read the document I am concerned that Ruxolitinib is apparently only going to be recommended for high risk patients when it would appear to be an effective drug for many MPN sufferers thereby hopefully stopping the progression of such MPN diseases which would in turn save further burdens on the NHS. I sincerely hope that the recommendations for this drug will extend to all relevant groups of patients.

Yours sincerely

[redacted]

Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Carer
Other role	
Organisation	
Location	England
Conflict	No
Notes	

Comments on individual sections of the ACD:

As a carer of someone who has had Myelofibrosis since 2013 and given 5 years to live, Ruxolitinib has been invaluable, improving symptoms and quality of life and hopefully will extend life beyond the 5 years prognosis. I am writing to add my voice of concern over funding issues and sincerely hope that Ruxolitinib will continue to be available as it has been giving us both hope for future. Don't make people wait until they are high risk. Thank you.

Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	

Comments on individual sections of the ACD:

I am an MPN patient, aged 42 years, have been diagnosed for 6, I know that my blood cancer will progress in the future and Ruxolitinib will most likely be my only option, I am currently on alternative treatments and these are not working well. I urge you to allow this drug to be available to ALL MPN Patients regardless of type or progression.

Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review	

of guidance)	

Name	[redacted] [redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD: Ruxolitinib should be available to patients at all stages of MF	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted] [redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD: why when we find a product that helps people with long term health issues, that helps why stop it, cost should not come into it if it helps people to extend there lift	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6	

(Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	

Comments on individual sections of the ACD:

I was informed that i was given Rux by [redacted] as soon as it was licensed in this country. I feel this timely intervention is the reason i'm alive today

As a patient diagnosed with Myelofibrosis in 1988 with a spleen removal in 1989 and a further removal of a spleneculous in 2000, i feel i am qualified to comment on the effectiveness of Ruxolitinib for me. I was put on Rux in August 2012 as a result of a deterioration in my condition. I was on it before i was given a SCT in May 2013. I had an immediate positive response when put on Rux, it gve me a feeling of welbeing and feeling 'better' I was able to continue with work and have an improved quality of life. I had no side affects and generally felt stronger, less tired and more able to live a fullfilling life. when the time came for my SCT i was in the best possible place for it to be successful. Once i was recovering from this procedure i was put back on Rux, it has made me feel 'well' again and gave me the opportunity to live a fairly normal life. Transfusions are still needed every 3 months but on the whole i feel good.

I don't think i would have felt as good as i do without Rux, it has enabled me to have a good quality of life and be able to live my life to the full, returning to work, enjoying leisure time and making the most of feeling 'better'. I would think every patient who might benefit from this drug, should be given the opportunity to have it prescribed allowing them a good quality of life. In my opinion this drug has reduced the amount of input i have needed by the NHS, i think more intense medical support would work out more expensive in the long run.

Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted] [redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	

Comments on individual sections of the ACD:
The decision to limit the availability of ruxolitinib is seriously misguided. The impact of this drug on people's QOL ensures that the NHS saves money because myelofibrosis patients require less other care. They also live longer. I was given it direct from the manufacturer and the positive impact on my life has been immense. I have become capable of work again and so contribute to the wealth of the country. Please reconsider.

Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted] [redacted]
Role	Public
Other role	
Organisation	
Location	England
Conflict	No
Notes	

Comments on individual sections of the ACD:
I am concerned that at present it seems ruxolitinib may only be approved for high risk patients. This is because the approved indication is for spleen reduction and symptoms regardless of disease stage. The clinical trials have shown that patients with intermediate risk disease benefit in these aspects but also importantly gain years of life with this drug.

This decision is based upon cost not upon effectiveness of ruxolitinib which NICE agrees with.

Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3	

(The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	

Comments on individual sections of the ACD:

was diagnosed with PMF in 2007 .It was discovered when I was a blood donor. I have an enlarged spleen and low hg. I have been taking 2 x 10mg Ruxolitinib a day since March 2013 and has improved my life tremendously.

Many of my symptons of MF have reduced and have felt much better on the drug. My hg is generally around 10 except when I get an infection, then it drops to around 9.

I still try and do 18 holes of golf and walk frequently.

I am 73 years of age and am trying to live as normal a life as possible and don't dwell on the fact I have an incurable disease.

Therefore I hope that I can continue to be a recipient of this marvellous drug.

Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Carer
Other role	

Organisation	
Location	England
Conflict	No
Notes	

Comments on individual sections of the ACD:
As a carer for an MPN patient I note from the consultation document that Ruxolitinib has been recommended for only high risk patients.

I believe it should also be recommended for other MPN patients if other treatments are not effective or cannot be tolerated by such patients.

Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Relative of patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	

Comments on individual sections of the ACD:
I understand the complex nature of the decisions that you are taking, decisions that have an impact on ordinary, less medically qualified than yourselves. For the future, a simple summary would be of great benefit.

On the personal level, I have watched my mother change from a person who looked, acted and felt ill to a person who is able to enjoy life and participate more fully; whilst understanding her fate. This change is all due to the provision of the drug treatment that you appear not to value highly enough to make available on a broad basis. I also understand that the drug will not cure my mother or others, so getting it to people early will only provide comfort, that is a big only. I have seen the difference that this drug has made to my mum and as a by product her family, she is still dying, we know that but with the provision of ruxilitinib things are more in her control and on her terms. I would urge the provision of treatment at the earliest opportunity to give the best standard of living from the earliest stage.

Section 1 (Appraisal Committee's	

preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD: Please allow Ruxolitinix to be available for all MPN patients at the discretion of their haematologists. It has been shown to be beneficial in many patients with PV and ET. So please do not restrict its use to MF only. PV and ET patients need sll the help they can get with this very troublesome disease.	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	NHS Professional
Other role	Community Cancer Nurse
Organisation	
Location	England
Conflict	No
Notes	

Comments on individual sections of the ACD: I have the pleasure of knowing an incredible lady who is benefiting from treatment with Ruxolitinib. It is given her quality and quantity of life . She lives life to the full and has been a massive driving force behind building a new Community Cancer Nursing Service HCCN. Without her we wouldn't be where we are now. If it wasn't for Ruxolitinib people like this lady wouldn't be able to make such a difference to others.	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD: MF patients need this drug to help reduce the spleen and other symptoms, regardless of the stage of the disease.	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Carer
Other role	

Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD: I have seen the impact of this drug for the past three years on my wife. Three years ago my wife was told that she probably had only a year to live after being diagnosed with myelofibrosis. The spleen had become massive and as result of this she had developed oesophageal varices. The impact of ruxalitinib was immediate and significant.Spleen size was greatly reduced enabling the resumption of an almost normal active life. Three years on the drug is still continuing to enable an active useful life. Ruxalitinib has given my wife at least two years of extra quality life. Why should others not be allowed from this remarkable drug treatment?	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD: wish to register my approval of Ruxolitinib for patients with Myelofibrosis. I have been on Ruxolitinib for 12 months and call it the "Miracle Drug". I was so poorly with continuing weight loss, fatigue, infections etc needing help with washing and dressing, struggling to get up each day and even making it through the day. I cannot praise this drug enough it has given me a new lease of life, my spleen has reduced in size, I have gained weight so do not need to take any nutrients and no longer see the Dietician, bloods have stabilised. Please feel free to contact me if I can be of any help.	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's	

submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Carer
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD: please make this available for all PV sufferers not just those with advanced MF.	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD: My mother-in-law was diagnosed with myelofibrosis in December 2010 aged 61. The doctors at the time gave her a prognosis of 2 to 5 years . When diagnosed, the size of her spleen meant that she had to make a large number of changes to her lifestyle (mainly around eating and sleeping). After a few months, she was admitted to hospital where she had to have transfusions and have a number of veins in her oesophagus tied. Soon after, she was put on ruxonitilib and the size of her spleen significantly decreased. the reduction in the size of her spleen has massively	

changed her quality of life. Even though the drug didn't cure the disease, the effects of the drug have been life changing. She managed to go back to living her life like before she was diagnosed and managed to do things she wouldn't have done before being put on the drug (travelling, making some more long-term plans, etc). For our family, the drug has made a massive difference with the myelofibrosis not being the limiting illness it was when she was first diagnosed. Her outlook on life changed dramatically and myelofibrosis became something you live with and not something that you wait to die from. She has been on the medication for 3 years now and i believe that the drug has allowed her to live longer and with a significantly better quality of life. This is why i believe that this drug should not be restricted to severely ill myelofibrosis patients but should be available as early as possible to increase their life-expectancy and quality of life.	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD: I live with an MPN and am very worried and concerned about the decisions NICE will make about approving Ruxolitinib. My understanding is that there is a possibility that this drug will only be approved for high risk patients. Clinical trials have shown that patients with intermediate risk benefit from taking this drug as it reduces spleen size and symptoms. Quality of life is vastly improved and more significantly a patient's life expectancy increases. We all know this is basically to do with drug costs. It is outrageous that pharmaceutical companies make so much profit . I wonder why there is so much research done to produce a life prolonging/saving drug, only to be told one is not sick enough and have to continue suffering until one becomes high risk. It is immoral and I do trust that NICE will give approval for Ruxolitinib to be available for all patients with MF.	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	

Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	Scotland
Conflict	No
Notes	
Comments on individual sections of the ACD: Please support condition sufferers who should receive best quality treatment thats been advanced for US and not government agencies cost cutting in interest of the economy	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Family member of a patient
Other role	
Organisation	
Location	Wales
Conflict	No
Notes	
Comments on individual sections of the ACD: It seems clear that as a family member of a person with pv that ruxolitinib should be available on a much wider scale to enable all people to gain its benefits and not just those where the disease has progressed. As it genuinely increases prospects and life then this must be available to all sufferers	
Section 1 (Appraisal Committee's	

preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD: I have been taking Ruxolitinib for 2 years and the difference to my life is emmence. in fact I never would have believed I could feel this well again. I now have my life back.	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD: I have PV that could develop into MF. I'm 45yrs old and want to see my grandchildren grow up. One day I might need this to help me be able to do this.	
Section 1 (Appraisal Committee's	

preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	I edit the newsletter for the patient group MPN Voice
Comments on individual sections of the ACD: s an MPN patient with regular contact with others who have his disease, I am disappointed to hear that this drug will only be available to MF patients in the end stages of their condition. Patients I have known with MF have a severely reduced quality of life and from the reports shared with patient groups, Ruxolitinib has been shown, not only to improve the debilitating symptoms, but extend the life span in these patients. I appreciate the demands on NICE to approve drugs based on cost and effectiveness but would add that if a patient with MF were your family member, wouldn't you want to have available a drug that would make them feel considerably better and live longer?	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]

Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD: I wish to thank NICE for considering this drug with such care. I have PVR and am in the MAJOC trial. Ruxolitinib is very easy to take. Please consider it for all of us with MPN disorders. I could no longer take hydroxy carbamide and would have had a harsher road to travel. Ruxolitinib is working well for me. I think it has a broader scope than MF urgency patients. I hope you won't leave patients until the urgency stage to grant the drug.	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisals

Patient access scheme submission

Ruxolitinib in myelofibrosis

1 Introduction

The 2009 Pharmaceutical Price Regulation Scheme (PPRS) (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the 2009 PPRS is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the features of the 2009 PPRS is to improve patients' access to medicines at prices that better reflect their value through patient access schemes.

Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient access schemes propose either a discount or rebate that may be linked to the number, type or response of patients, or a change in the list price of a medicine linked to the collection of new evidence (outcomes). These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the 2009 PPRS (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS.

Patient access schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

2 Instructions for manufacturers and sponsors

This document is the patient access scheme submission template for technology appraisals. If manufacturers and sponsors want the National Institute for Health and Care Excellence (NICE) to consider a patient access scheme as part of a technology appraisal, they should use this template. NICE can only consider a patient access scheme after formal referral from the Department of Health.

The template contains the information NICE requires to assess the impact of a patient access scheme on the clinical and cost effectiveness of a technology, in the context of a technology appraisal, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal' (http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9)
- 'Specification for manufacturer/sponsor submission of evidence' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/singletechnologyappraisalsubmissiontemplates.jsp) and
- Pharmaceutical Price Regulation Scheme 2009 (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS).

For further details on the technology appraisal process, please see NICE's 'Guide to the single technology appraisal (STA) process' and 'Guide to the multiple technology appraisal (MTA) process' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp). The

‘Specification for manufacturer/sponsor submission of evidence’ provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme. Send submissions electronically to NICE in Word or a compatible format, not as a PDF file.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a patient access scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme incorporated, in accordance with the ‘Guide to the methods of technology appraisal’ (http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9).

If you are submitting the patient access scheme at the end of the appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

3 Details of the patient access scheme

3.1 Please give the name of the technology and the disease area to which the patient access scheme applies.

Technology: ruxolitinib (Jakavi®)

Disease area: myelofibrosis

3.2 Please outline the rationale for developing the patient access scheme.

The simple discount scheme was developed to improve the cost-effectiveness of ruxolitinib and enable patients to receive access this innovative medicine

3.3 Please describe the type of patient access scheme, as defined by the PPRS.

Simple discount scheme

3.4 Please provide specific details of the patient population to which the patient access scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? If so:

- How is the subgroup defined?
- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

The patient access scheme will apply to the full licensed population, which is also the population covered by the STA submission: 'the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis'

3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

The scheme applies to all eligible patients from the time of treatment initiation

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

All patients eligible for treatment with ruxolitinib as per the licensed indication will meet the scheme criteria

3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

The confidential PAS price will be applied directly on the original invoice produced by Novartis to the purchasing organization at the point of positive NICE guidance. The scheme does not increase administrative burden to the NHS and there will be no need for rebates for be calculated and paid.

The scheme will operate as a fixed price scheme (which will not vary with any change to the UK list price), therefore the % discount could vary. However, at the current list price, the discount will be [redacted]%.

	Cost per 56-tablet blister pack (excluding VAT)	
	List price	With PAS
5 mg	£1,680	[redacted]
10 mg	£3,360	[redacted]
15 mg	£3,360	[redacted]
20 mg	£3,360	[redacted]

3.8 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

As a simple discount provided at the point of invoice, there are no administration requirements. No additional information will be collected.

3.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.

The PAS price will be applied directly to the original invoice and the scheme will therefore operate no differently from any other order placed by an NHS hospital.

3.10 Please provide details of the duration of the scheme.

The scheme will be in place from the date of guidance publication and until NICE next reviews the guidance on the product and a final decision has been published on the NICE website

3.11 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

There are no equity or equalities issues relating to the scheme

3.12 If available, please list any scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians and patient information documents. Please include copies in the appendices.

There are no forms associated with the provision of this simple discount.

3.13 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix B.

4 Cost effectiveness

4.1 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main manufacturer/sponsor submission of evidence for the technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for manufacturer/sponsor submission of evidence' (particularly sections 5.5, 6.7 and 6.9). You should complete those sections both with and without the patient access scheme. You must also complete the rest of this template.

The scheme applies to the same population as that presented in the main submission of evidence for the STA

4.2 If you are submitting the patient access scheme at the end of the technology appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

Not applicable

4.3 Please provide details of how the patient access scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the Appraisal Committee considered most plausible.

The daily cost of ruxolitinib has been reduced by [redacted]%

4.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the patient access scheme.

Not applicable – not an outcomes-based scheme

4.5 Please list any costs associated with the implementation and operation of the patient access scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. Please refer to section 6.5 of the 'Specification for manufacturer/sponsor submission of evidence'.

No additional costs are associated with the implementation and operation of the patient access scheme.

4.6 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

No additional treatment-related costs are incurred by implementing the patient access scheme.

Summary results

Base-case analysis

4.7 Please present in separate tables the cost-effectiveness results as follows.[1]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

A suggested format is shown below (table 3).

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

Base case results without the PAS are presented in Table 1. Compared with BAT, the ICER for ruxolitinib therapy was £[redacted] per QALY gained without the PAS.

Table 1 Base-case cost-effectiveness results (without the PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
BAT	£[redacted]	[redacted]	[redacted]				£[redacted]	
Ruxolitinib	£[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]

With the PAS, the ICER for ruxolitinib therapy was £44,905 per QALY gained.

Table 2 Base-case cost-effectiveness results (with the PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
BAT	£36,271	2.15	1.476				£24,577	
Ruxolitinib	£149,114	5.96	3.989	£112,843	3.81	2.51	£37,384	£44,905

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

4.8 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4.

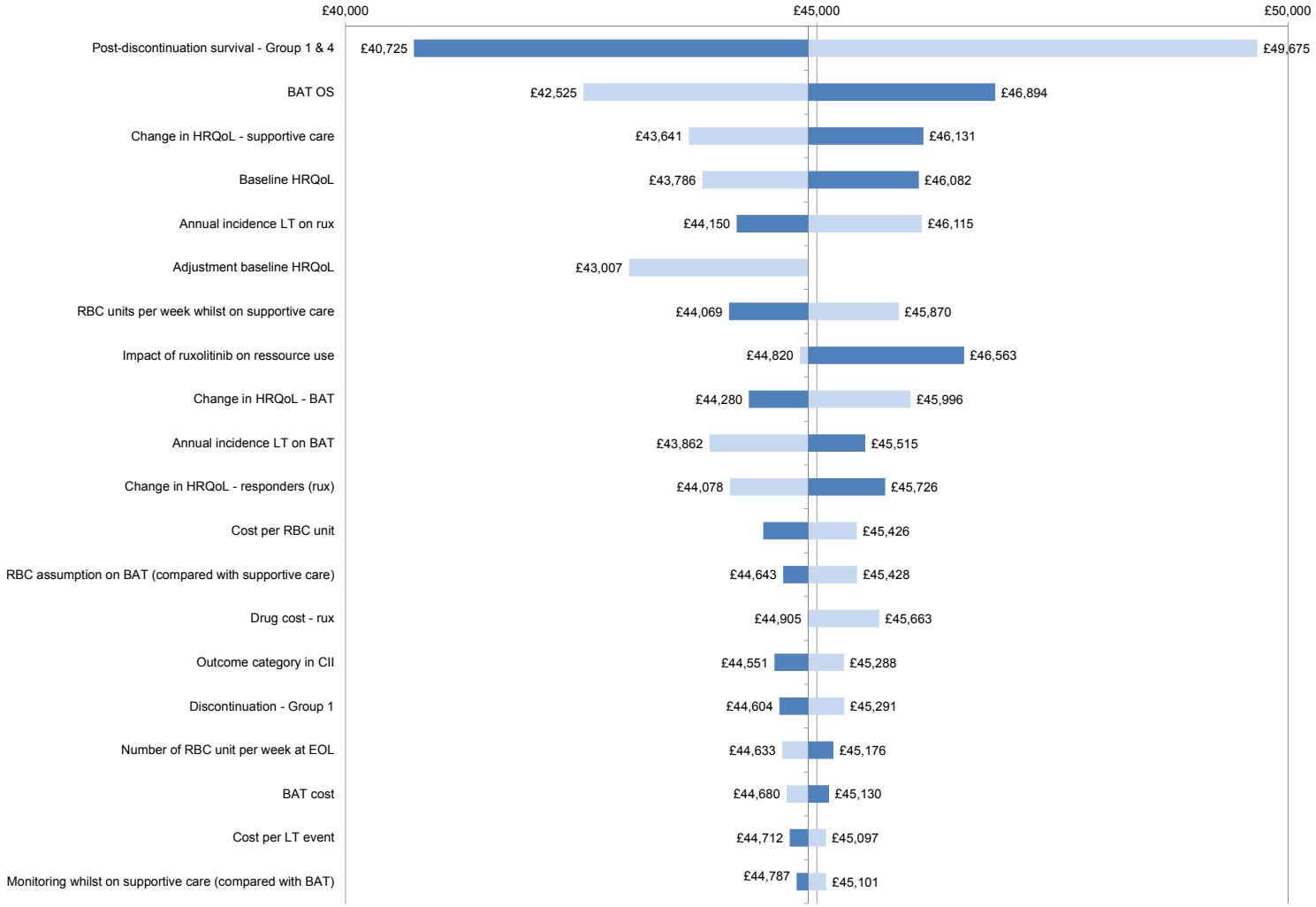
[2] For outcome-based schemes, please see section 5.2.9 in appendix B.

Not applicable – only one comparator and one intervention

Sensitivity analyses

4.9 Please present deterministic sensitivity analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal. Consider using tornado diagrams.

Figure 1 Univariate sensitivity analysis



4.10 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

The ICER is £44,625 per QALY gained in the probabilistic sensitivity analysis (with the PAS).

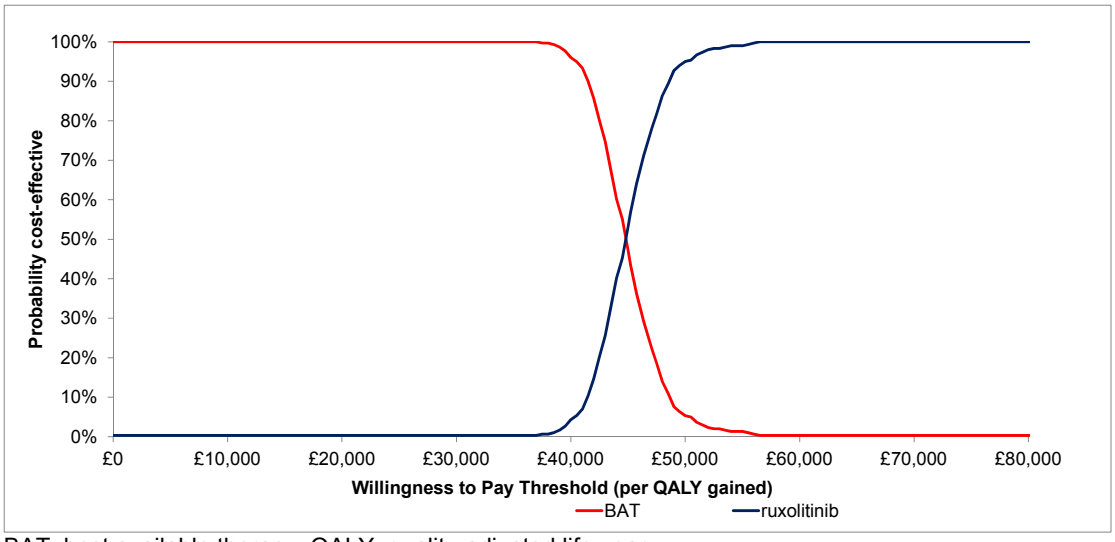
Table 3 Results of the probabilistic sensitivity analysis

	Life years (undiscounted)	QALYs (discounted)	Cost (discounted)	ICER
Ruxolitinib	6.12	4.04	£150,794	
BAT	2.16	1.48	£36,349	
Incremental	3.96	2.56	£114,445	£44,625

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

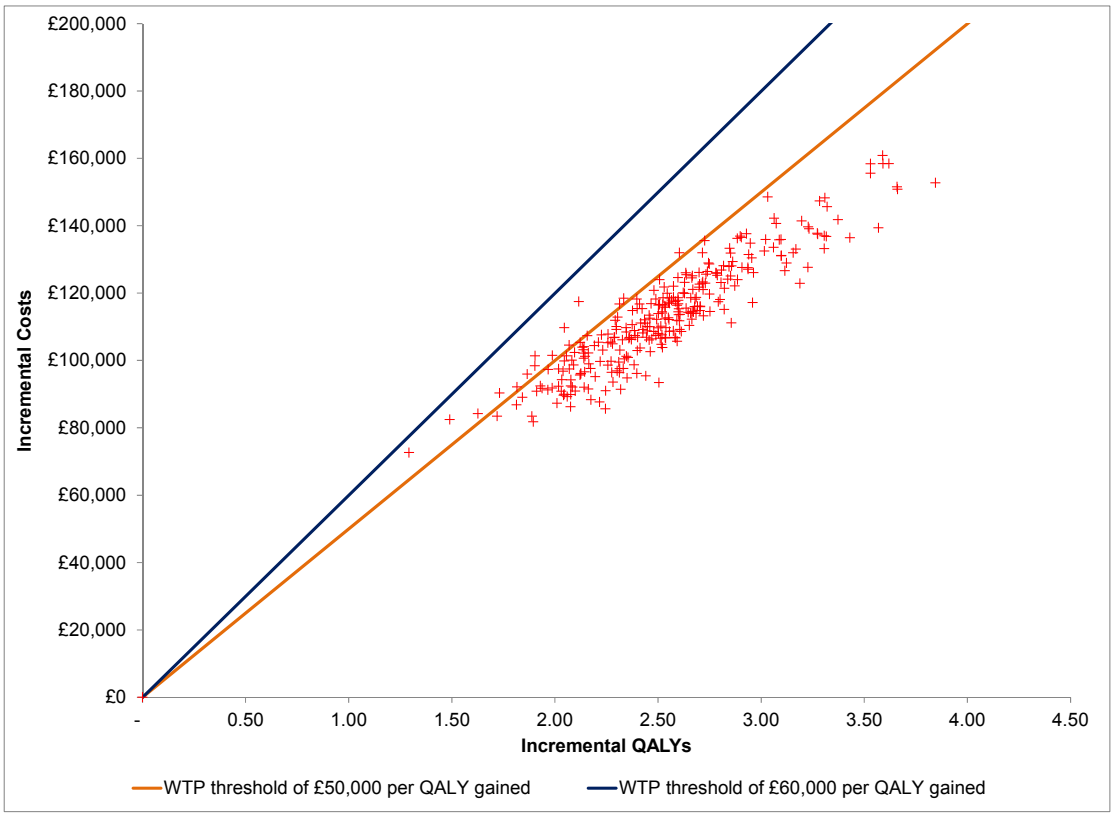
Figure 2 and Figure 3 show the cost effectiveness plane and cost effectiveness acceptability curve using results generated over a lifetime horizon. The curves show the probability of being cost effective for different levels that the decision maker may be willing to pay for an additional QALY. The cost effectiveness acceptability curves show that the probability of ruxolitinib being is a cost-effective strategy is 0.33%, 4.32%, 95.02% and 100% when using a threshold of £30,000, £40,000, £50,000 and £60,000 per QALY, respectively.

Figure 2 Cost effectiveness acceptability curves



BAT, best available therapy; QALY, quality-adjusted life year.

Figure 3 Cost effectiveness plane



QALY, quality-adjusted life year. WTP, willingness to pay threshold

4.11 Please present scenario analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal.

Results are presented with the PAS

Time horizon

Table 4 Scenario analysis 1: reducing the time horizon

	Ruxolitinib			BAT			
Description	**Life years**	**QALYs**	**costs**	**Life years**	**QALYs**	**costs**	**ICER**
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
Time horizon = 5 years	3.642	2.761	£112,469	2.153	1.475	£36,264	£59,266
Time horizon = 10 years	5.077	3.615	£138,399	2.154	1.476	£36,271	£47,730
Time horizon = 15 years	5.659	3.885	£146,171	2.154	1.476	£36,271	£45,625
Time horizon = 20 years	5.860	3.960	£148,284	2.154	1.476	£36,271	£45,096

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

BAT discontinuation

Table 5 Scenario analysis 2: BAT discontinuation – parametric curves

	Ruxolitinib			BAT			
Description	**Life years**	**QALYs**	**costs**	**Life years**	**QALYs**	**costs**	**ICER**
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
BAT discontinuation = exponential	5.959	3.986	£149,099	2.151	1.466	£36,205	£44,799
BAT discontinuation = Weibull	5.960	3.988	£149,136	2.153	1.472	£36,239	£44,874
BAT discontinuation = Log-normal	5.962	3.988	£149,139	2.151	1.466	£36,369	£44,706

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

Table 6 Scenario analysis 3: Duration on BAT

Description	Ruxolitinib			BAT			ICER
	Life years	**QALYs**	**costs**	**Life years**	**QALYs**	**costs**	
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
BAT discontinuation reduced by 10%	5.960	3.990	£149,123	2.154	1.479	£36,356	£44,920
BAT discontinuation reduced by 20%	5.960	3.991	£149,158	2.154	1.483	£36,444	£44,947
BAT discontinuation reduced by 30%	5.960	3.991	£149,212	2.154	1.487	£36,520	£44,994
BAT discontinuation reduced by 40%	5.959	3.992	£149,237	2.154	1.491	£36,676	£44,996

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

OS in patients treated under current practice (ie in the absence of ruxolitinib)

Table 7 Scenario analysis 4: overall survival for BAT corrected for crossover: parametric survival distributions

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
BAT OS (cross-over adjusted) = exponential	6.732	4.356	£153,424	5.055	2.864	£52,560	£67,633
BAT OS (cross-over adjusted)= Weibull	6.034	4.032	£149,612	2.432	1.639	£37,941	£46,676
BAT OS (cross-over adjusted)= Log-normal	6.807	4.383	£153,792	5.335	2.965	£54,046	£70,371

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality-adjusted life year.

Table 8 Scenario analysis 5: overall survival for BAT, COMFORT-II, intention-to-treat: parametric survival distributions

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
BAT OS (ITT)= Weibull	6.584	4.298	£152,657	4.498	2.648	£49,685	£62,391
BAT OS (ITT)= Gompertz	6.431	4.233	£151,810	3.924	2.402	£46,492	£57,507

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; OS, overall survival; QALY, quality-adjusted life year.

Post-BAT discontinuation survival

Table 9 Scenario analysis 6: Shape of the post-BAT survival curve

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
BAT post-discontinuation survival (shape of Weibull = -1)	5.917	3.907	£148,627	2.075	1.191	£34,841	£41,885
BAT post-discontinuation survival (shape of Weibull = -0.8)	5.934	3.928	£148,820	2.124	1.269	£35,366	£42,659
BAT post-discontinuation survival (shape of Weibull = -0.6)	5.941	3.946	£148,922	2.143	1.332	£35,775	£43,294

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
BAT post-discontinuation survival (shape of Weibull = -0.4)	5.947	3.959	£149,005	2.150	1.381	£35,963	£43,844
BAT post-discontinuation survival (shape of Weibull = -0.2)	5.951	3.969	£149,060	2.151	1.415	£36,107	£44,229
BAT post-discontinuation survival (shape of Weibull = 0)	5.954	3.977	£149,069	2.152	1.439	£36,219	£44,473
BAT post-discontinuation survival (shape of Weibull = 0.2)	5.956	3.982	£149,093	2.152	1.456	£36,184	£44,697
BAT post-discontinuation survival (shape of Weibull = 0.4)	5.958	3.986	£149,115	2.153	1.467	£36,226	£44,823
BAT post-discontinuation survival (shape of Weibull = 0.6)	5.959	3.988	£149,113	2.154	1.475	£36,258	£44,899
BAT post-discontinuation survival (shape of Weibull = 0.8)	5.961	3.990	£149,122	2.154	1.480	£36,300	£44,947
BAT post-discontinuation survival (shape of Weibull = 1)	5.962	3.992	£149,156	2.155	1.485	£36,303	£45,006

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

Table 10 Scenario analysis 7: Examining structural assumption regarding the estimate for post-BAT survival

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
Approach 1: BAT OS and discontinuation sampled (discontinuation adjusted)	5.965	3.991	£149,105	2.162	1.477	£36,252	£44,899
Approach 2: BAT OS and discontinuation sampled (OS adjusted)	5.981	4.002	£149,226	2.215	1.515	£36,681	£45,255
Approach 3: BAT post-discontinuation survival calibrated	5.959	3.990	£149,131	2.146	1.478	£36,257	£44,925

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality-adjusted life year.

Response criteria

Table 11 Scenario analysis 8: response criteria

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
Response definition (≥50% spleen reduction & ≥25% MF-SAF reduction)	6.351	4.220	£160,215	2.154	1.476	£36,271	£45,169
Response definition (≥25% spleen reduction & ≥50% MF-SAF reduction)	6.358	4.141	£156,204	2.154	1.475	£36,271	£44,992
Response definition (≥25% spleen reduction & ≥25% MF-SAF reduction)	6.613	4.292	£162,896	2.154	1.476	£36,271	£44,966
Response definition (≥50% spleen reduction & ≥ upper MID FACT-Lym)	5.923	3.965	£148,159	2.154	1.476	£36,271	£44,952
Response definition (≥50% spleen reduction & ≥ lower MID FACT-Lym)	6.421	4.267	£162,161	2.154	1.476	£36,271	£45,112
Response definition (≥25% spleen reduction & ≥ upper MID FACT-Lym)	6.412	4.173	£157,552	2.154	1.475	£36,271	£44,952
Response definition (≥25% spleen reduction & ≥ lower MID FACT-Lym)	6.752	4.382	£166,957	2.154	1.476	£36,271	£44,981

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

Ruxolitinib discontinuation

Table 12 Scenario analysis 9: ruxolitinib discontinuation rates in patients a spleen response; parametric survival distributions

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
Discontinuation responder (Group1) = Weibull	5.836	3.922	£146,245	2.154	1.476	£36,271	£44,955

Discontinuation responder (Group1) = Gompertz	6.058	4.039	£151,293	2.154	1.476	£36,271	£44,875
Discontinuation responder (Group1) = Log-normal	7.590	4.766	£183,231	2.154	1.476	£36,271	£44,665

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

Table 13 Scenario analysis 10: Maximum duration on ruxolitinib

	Ruxolitinib			BAT			ICER
Description	**Life years**	**QALYs**	**costs**	**Life years**	**QALYs**	**costs**	
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
Ruxolitinib is stopped at 3.5 years	4.350	2.947	£103,869	2.154	1.476	£36,271	£45,954
Ruxolitinib is stopped at 5 years	4.787	3.266	£117,804	2.154	1.476	£36,271	£45,532
Ruxolitinib is stopped at 7 years	5.277	3.602	£132,337	2.154	1.476	£36,271	£45,188
Ruxolitinib is stopped at 10 years	5.569	3.785	£140,334	2.154	1.476	£36,271	£45,058

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

Survival post-ruxolitinib discontinuation

Table 14 Scenario analysis 11: survival following ruxolitinib discontinuation (pooled); parametric survival distributions

Description	**Ruxolitinib**			**BAT**			**ICER**
	Life years	**QALYs**	**costs**	**Life years**	**QALYs**	**costs**	
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
Post-discontination survival (rux) - Weibull	6.108	4.021	£149,689	2.154	1.476	£36,271	£44,555
Post-discontination survival (rux) - log-normal	7.902	4.239	£155,102	2.154	1.476	£36,271	£42,998

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; PPS, QALY, quality-adjusted life year.

Table 15 Scenario analysis 12: Maximum duration alive post-ruxolitinib discontinuation

	Ruxolitinib			BAT			
Description	**Life years**	**QALYs**	**costs**	**Life years**	**QALYs**	**costs**	**ICER**
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
post-discontinuation maximum = 3.5 years	5.441	3.828	£146,992	2.154	1.476	£36,271	£47,081
post-discontinuation maximum = 5 years	5.663	3.915	£147,964	2.154	1.476	£36,271	£45,789
post-discontinuation maximum = 7.5 years	5.845	3.971	£148,712	2.154	1.476	£36,271	£45,066
post-discontinuation maximum = 10 years	5.916	3.985	£148,987	2.154	1.476	£36,271	£44,923

Table 16 Scenario analysis 13: survival following ruxolitinib discontinuation in patients achieving a spleen response; parametric survival distributions

Description	**Ruxolitinib**			**BAT**			**ICER**
	Life years	**QALYs**	**costs**	**Life years**	**QALYs**	**costs**	
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
Separate post-discontinuation survival (Group 1 & 4) - exponential	6.010	4.008	£149,355	2.154	1.476	£36,271	£44,667
Separate post-discontinuation survival (Group 1 & 4) - Weibull	6.185	4.042	£150,020	2.154	1.476	£36,271	£44,320
Separate post-discontinuation survival (Group 1 & 4) - log-normal	7.895	4.241	£155,095	2.154	1.476	£36,271	£42,968

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

Table 17 Scenario analysis 14: survival following ruxolitinib discontinuation in patients not achieving response

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
Reduced survival for patients on ruxolitinib (Group 3)	5.892	3.943	£148,582	2.154	1.476	£36,271	£45,526

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

Leukaemic transformation

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Table 18 Scenario analysis 15: leukaemic transformation

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
Incidence of LT assumed to be the same	5.960	3.980	£151,682	2.154	1.476	£36,271	£46,089
Removal of LT	5.960	3.999	£145,979	2.154	1.485	£33,727	£44,634

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

Assumptions regarding HRQoL

Table 19 Scenario analysis 16: HRQoL measure

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
HrQoL measured using the MF-8Dv2	5.960	3.725	£149,114	2.154	1.349	£36,271	£47,499
HrQoL measured using the EQ-5D	5.960	3.853	£149,114	2.154	1.468	£36,271	£47,313

BAT, best available therapy; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Table 20 Scenario analysis 17: HRQoL assumptions while on BAT

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
Change in HRQoL for BAT = half change in supportive care	5.960	3.982	£149,114	2.154	1.452	£36,271	£44,590
Change in HRQoL for BAT = 1/3 change in supportive care	5.960	3.985	£149,114	2.154	1.460	£36,271	£44,694
Change in HRQoL for BAT = 1/4 change in supportive care	5.960	3.986	£149,114	2.154	1.464	£36,271	£44,747
Change in HRQoL for BAT = half change on ruxolitinib	5.960	4.031	£149,114	2.154	1.636	£36,271	£47,120
Change in HRQoL for BAT = 1/3 change on ruxolitinib	5.960	4.017	£149,114	2.154	1.583	£36,271	£46,358
Change in HRQoL for BAT = 1/4 change on ruxolitinib	5.960	4.010	£149,114	2.154	1.556	£36,271	£45,986

BAT, best available therapy; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; QoL, quality of life.

Table 21 Scenario analysis 18: HRQoL assumptions while on placebo

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
Progression of HRQoL on supportive care halved after 24 weeks	5.960	4.070	£149,114	2.154	1.489	£36,271	£43,726
Progression of HRQoL on supportive care halved after 48 weeks	5.960	4.055	£149,114	2.154	1.482	£36,271	£43,870
Progression of HRQoL on supportive care halved after 72 weeks	5.960	4.042	£149,114	2.154	1.479	£36,271	£44,015

BAT, best available therapy; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Table 22 Scenario analysis 19: short-term HRQoL assumptions while on ruxolitinib

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
Patients on ruxolitinib experience an improvement in HrQoL at 8 weeks	5.960	3.980	£149,114	2.154	1.476	£36,271	£45,055
Patients on ruxolitinib experience an improvement in HrQoL at 12 weeks	5.960	3.972	£149,114	2.154	1.476	£36,271	£45,206
Patients on ruxolitinib experience an improvement in HrQoL at 16 weeks	5.960	3.964	£149,114	2.154	1.476	£36,271	£45,356
Patients on ruxolitinib experience an improvement in HrQoL at 20 weeks	5.960	3.955	£149,114	2.154	1.476	£36,271	£45,507

BAT, best available therapy; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Table 23 Scenario analysis 20: long-term HRQoL progression assumption while on ruxolitinib

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
Patients on ruxolitinib do not maintain their initial gain in HrQoL	5.960	3.799	£149,114	2.154	1.476	£36,271	£48,569
25% reduction in gain in HRQoL every 52 weeks for patients on ruxolitinib	5.960	3.805	£149,114	2.154	1.476	£36,271	£48,441

BAT, best available therapy; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Table 24 Scenario analysis 21: structural assumptions regarding HRQoL

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
Constant HrQoL	5.960	4.154	£149,114	2.154	1.498	£36,271	£42,486

BAT, best available therapy; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Assumptions regarding red blood cell transfusion units

Table 25 Scenario analysis 22: assumptions regarding RBC transfusions

	Ruxolitinib			BAT			
Description	**Life years**	**QALYs**	**costs**	**Life years**	**QALYs**	**costs**	**ICER**
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
No impact of ruxolitinib on RBC units	5.960	3.989	£150,735	2.154	1.476	£36,271	£45,550
Ruxolitinib is associated with a 5% increase in RBC units over the lifetime	5.960	3.989	£151,178	2.154	1.476	£36,271	£45,726
Increase in RBC units by 5% every 24 weeks for patients on supportive care	5.960	3.989	£150,082	2.154	1.476	£36,794	£45,082

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; RBC, red blood cell; QALY, quality-adjusted life year.

Discount rates

Table 26 Scenario analysis 23: discount rate

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
Discount rate (1.5% cost)	5.960	3.989	£160,949	2.154	1.476	£37,224	£49,235
Discount rate (1.5% QALYs)	5.960	4.305	£149,114	2.154	1.498	£36,271	£40,201
Discount rate (both 1.5%)	5.960	4.305	£160,949	2.154	1.498	£37,224	£44,077

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

4.12 If any of the criteria on which the patient access scheme depends are clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the Appraisal Committee can determine which criteria are the most appropriate to use.

Not applicable

Impact of patient access scheme on ICERs

4.13 For financially based schemes, please present the results showing the impact of the patient access scheme on the ICERs for the base-case and any scenario analyses. A suggested format is shown below (see table 5). If you are submitting the patient access scheme at the end of the appraisal process, you must include the scenario with the assumptions that the Appraisal Committee considered to be most plausible.

Results with the PAS (base case and scenario analysis) are presented above. Results without the PAS are available in the original NICE submission.

5 Appendices

5.1 Appendix A: Additional documents

5.1.1 If available, please include copies of patient access scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians, patient information documents.

No forms of additional documents are required for the operation of this Patient Access Scheme

5.2 Appendix B: Details of outcome-based schemes

5.2.1 If you are submitting a proven value: price increase scheme, as defined in the PPRS, please provide the following information:

- the current price of the intervention
- the proposed higher price of the intervention, which will be supported by the collection of new evidence
- a suggested date for when NICE should consider the additional evidence.

Response

5.2.2 If you are submitting an expected value: rebate scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the planned lower price of the intervention in the event that the additional evidence does not support the current price
- a suggested date for when NICE should consider the additional evidence.

Response

5.2.3 If you are submitting a risk-sharing scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the proposed relationship between future price changes and the evidence to be collected.

Response

5.2.4 For outcome-based schemes, as defined in the PPRS, please provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study
- outcomes of the new study
- expected duration of data collection
- planned statistical analysis, definition of study groups and reporting (including uncertainty)
- expected results of the new study
- planned evidence synthesis/pooling of data (if applicable)
- expected results of the evidence synthesis/pooling of data (if applicable).

Response

5.2.5 If you are submitting a risk-sharing scheme, please specify the period between the time points when the additional evidence will be considered.

Response

5.2.6 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered.

Response

5.2.7 Please provide the other data used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

Response

5.2.8 Please present the cost-effectiveness results as follows.

- For proven value: price increase schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For expected value: rebate schemes, please summarise in separate tables:
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming).
- For risk-sharing schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming)
  - the anticipated results based on the expected new evidence and the proposed higher price.

A suggested format is shown in table 3, section 4.7.

5.2.9 Please present in separate tables the incremental results for the different scenarios as described above in section 5.2.8 for the type of outcome-based scheme being submitted.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4, section 4.8.

National Institute for Health and Care Excellence

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

RESPONSE TO APPRAISAL CONSULTATION DOCUMENT: APPENDIX

10 November 2015

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1 Summary

The manufacturer provided a submission in which the base case incremental cost-effectiveness ratio (ICER) for ruxolitinib including a patient access scheme (PAS) was £44,905 per quality-adjusted life years (QALY) gained. This was based on an analysis using data from the COMFORT-II trial which included a mixed population of patients with intermediate-2 and high risk myelofibrosis (MF). The Appraisal Committee (AC) concluded that (a) the most plausible ICER for patients with intermediate-2 or high risk MF was in the region of £45,000 per QALY gained and that (b) only high risk patients met all the end-of-life criteria and that additional weightings would apply to this population.

As a result, the Committee's preliminary recommendation is that ruxolitinib is approved as an option for the treatment of patients with high risk MF providing the agreed PAS is in place.

Patients with intermediate-2 MF also have a significant umet treatment need and the phase 3 studies have shown the benefit of ruxolitinib treatment in this sub-group both in terms of improvement in symptoms, quality of life and life expectancy.

The evidence review group (ERG) identified minor programming errors and commented on the fact that some of the assumptions used in the original manufacturer's base case were conservative and likely to over-estimate the ICER.

Consequently, in order to provide the most accurate estimate of the ICER, the base case presented by the manufacturer in the original submission to NICE (£44,905) has been revised to account for (a) errors identified by the ERG on the inclusion of leukaemic transformation (LT) in the economic model, (b) adjusting the baseline utility (c) change to the treatment pathways for responders to ruxolitinib and (d) the exclusion of lenolidomide.

A revised PAS has also been offered by Novartis.

These changes result in a revised base case ICER for ruxolitinib of £31,385 per QALY gained (including the revised PAS). The ICER is £31,240 per QALY gained in the probabilistic sensitivity analysis (with the revised PAS).

We believe that additional factors also need to be considered.

- **Impact of MF on caregivers' quality of life**. An exploratory analysis illustrates that, under a series of assumptions regarding the impact of MF on caregiver quality of life, the revised base case ICER (including PAS) can be reduced to £28,111 per QALY gained.
- **Economic impact of MF on patients and carers**. Various European studies have shown that MF can have a considerable economic impact on patients and their carers,

both in terms of time devoted to caring by informal carers and loss of earnings for both patients and carers.

- **Additional weighting due to end-of-life for the mixed population of patients with high and intermediate-2 risk MF**. Data indicate the the survival of the combined group is in the region of 2 years from time of treatment initiation and therefore the full group could meet end-of-life criteria.

- **Additional consideration when assessing the mixed population**: consideration should be given to the fact that the Appraisal Committee has agreed that approximately half the population meets end-of-life criteria. As a result, the threshold against which cost-effectiveness for the whole group is assessed should be between £30,000 and £50,000.

REVISED ASSUMPTIONS AND ADDITIONAL CONSIDERATIONS

In addition to minor programming errors (inclusion of LT), the ERG highlighted two key areas of uncertainty in the economic model which were deemed to over-estimate the base case ICER: (a) absence of adjustment to the baseline utility and (b) assuming responders to ruxolitinib to move directly to supportive care. In contrast, the ERG also highlighted that the inclusion of lenalidomide was not relevant to UK clinical practice and could underestimate the ICER; this point was accepted by the AC.

In order to provide the most accurate estimate of the ICER, the base case was revised to address these points and a revised PAS has also been offered by the manufacturer.

2 Description of the changes

The following changes were made to the model (version provided on 27 July 2015 in response to clarification questions):

a) Correction of the errors identified by the ERG on formula for the inclusion of LT (section 5.2.10.1 of the ERG report)

Formulas were amended as per ERG suggested code.

b) Adjusting baseline utility by a factor of 10% (section 5.2.6.1 of the ERG report)

As noted in our original submission, although patients enrolled in the two COMFORT trials are broadly similar, patients in COMFORT-I had to be resistant or refractory to, intolerant of, or, in the investigator's opinion, not candidates for available therapy, suggesting that the population may have had slightly more severe symptoms and a worse health-related quality of life (HRQoL) compared with patients enrolled in COMFORT-II. In addition, patients in COMFORT-I had larger spleens (by length and volume) as well as worse Eastern Cooperative Oncology Group (ECOG) performance at baseline.

As the economic analysis is based on COMFORT-II, taking the baseline utility from COMFORT-I is likely to underestimate the baseline quality of life in the economic model; this point was accepted by the ERG in Section 5.2.6.1. In our original base-case no adjustment was made to limit the number of assumptions in the economic model. However, the ERG highlighted in section 5.2.6.1 of their report that adjusting the baseline utility value will *"lower the ICER estimate by several £1,000s per QALY and may represent a more realistic estimate of ICER for ruxolitinib"*

Consequently, the baseline quality of life was adjusted in our revised base-case as recommended by the ERG in order to provide a most accurate estimate of the ICER.

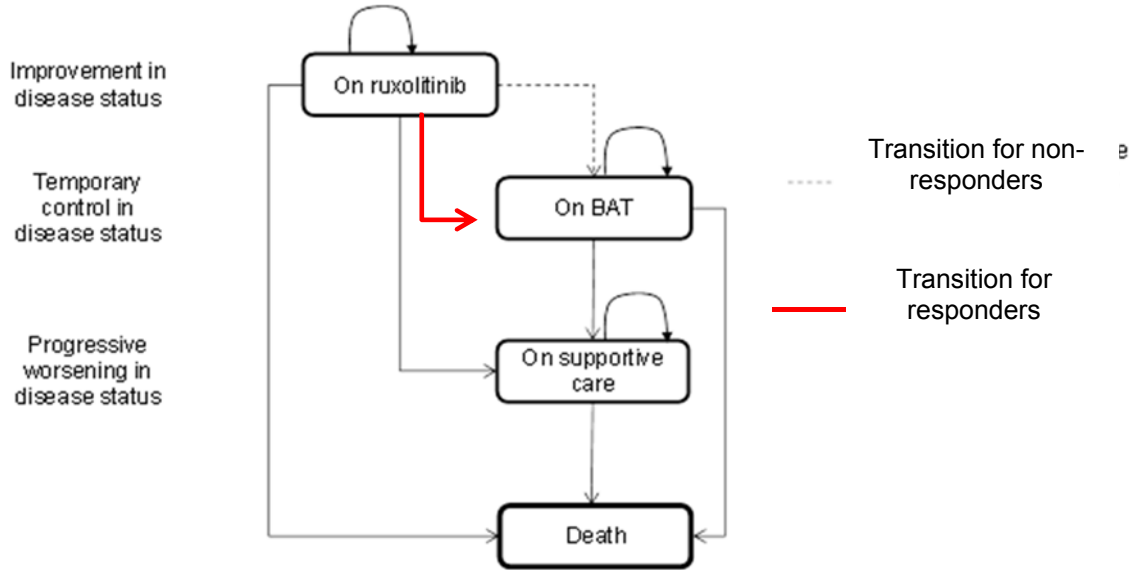
The degree of under-estimation of the baseline utility is uncertain as quality of life was not collected in the COMFORT-II trial. In order to provide an estimate, a clinical expert was asked to provide an indication of the possible under-estimation.[1] The clinical expert indicated that an adjustment factor of 10% could be appropriate given that patients in COMFORT-I were refractory to best available therapy (BAT) at entry to the trial. Hence, to account for the possible differences in baseline HRQoL between COMFORT-I and COMFORT-II, the baseline score in COMFORT-I was uplifted by 10% in the base case supported by clinical opinion.

c) Assuming responders spend time on BAT after ruxolitinib discontinuation

In Section 5.2.1 of the ERG report it is stated that *"The transition path of the four groups was considered largely to be plausible and representative of the clinical pathway. As acknowledged in the CS the transition of treatment responders directly to supportive care may not be representative of clinical practice and at least a proportion of these patients are likely to go on to receive BAT therapy. This assumption is, however, a conservative one and likely to lead to an overestimation of the ICER.*

In order to explore relaxing this assumption, we assumed that responders would spend a proportion of their time post-ruxolitinib on BAT before moving to supportive care, as depicted in Figure 1 (red line).

Figure 1 Updated simplified schematic of the model structure



BAT, best available therapy.

Patients initiating BAT when not previously exposed to ruxolitinib remain in the model approximately 45% of their time alive on BAT (based on the COMFORT-II trial). As no data are available to inform the proportion of time responders spend on BAT, a conservative assumption was used in the model assuming that responders on ruxolitinib would spend 30% of their time alive post ruxolitinib cessation on BAT.

d) Exclusion of lenalidomide

The ERG questioned the inclusion of lenalidomide in the BAT basket when estimating the cost for BAT. During the clarification response, the ERG requested an analysis in which patients receiving lenalidomide would receive hydroxyurea instead.

We consider that it is unlikely that patients receiving lenalidomide would instead receive hydroxyurea.

The British Committee for Standards in Haematology (BCSH) guidelines (Reilly 2012)[2] recommend hydroxyurea for the medical management of splenomegaly only in the absence of cytopenias. Doses of more than 1.5 g/d may be required to achieve clinical effect and that side effects, especially significant cytopenias, may be problematic at effective doses.

The BSCH guidelines acknowledge that there are limited published data supporting the efficacy of hydroxyurea, and note that complete responses are rare.

In the presence of cytopenias, the BSCH guidelines recommend use of thalidomide or lenalidomide. In our revised base case, lenalidomide was therefore replaced with thalidomide which is more in line with UK guidelines.

We would like to point out that, while usage of lenalidomide in the UK is very small, it is occasionally prescribed for MF patients. Market research carried out indicated that, in 2014, approximately 3% of MF patients in the UK were treated with lenalidomide.[3]

e) Revised PAS

A revised PAS (discount of [redacted]%) has also been offered to the NHS.

2.1 Results

For transparency, results are presented with the revised PAS under (a) the previous base case assumptions and (b) the revised base case assumptions (corrections of errors and addressing some of the concerns expressed by the ERG).

2.1.1 Deterministic ICER

2.1.1.1 Original base case with revised PAS

Using the revised PAS (discount of [redacted]%) the model predicted that, over a lifetime, for patients initiating treatment on ruxolitinib, the discounted incremental QALYs were 2.51 and discounted incremental costs were £87,633 compared to BAT. The ICER for ruxolitinib therapy was £34,865 per QALY gained.

Table 1 Base-case ICER under the revised PAS and original base-case

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
BAT	£36,238	1.476			
Ruxolitinib	£123,872	3.989	£87,633	2.51	£34,865

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; QALY, quality-adjusted life years

2.1.1.2 Revised base case with the PAS

Using the revised PAS (discount of [redacted]%) and correcting for errors identified by the ERG, the model predicted that, over a lifetime, for patients initiating treatment on ruxolitinib, the

discounted incremental QALYs were 2.82 and discounted incremental costs were £88,502 compared to BAT. The ICER for ruxolitinib therapy was £31,385 per QALY gained.

Table 2 Base-case ICER under the revised PAS and revised base-case

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
BAT	£35,422	1.628			
Ruxolitinib	£123,923	4.448	£88,502	2.82	£31,385

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; QALY, quality-adjusted life years

2.1.2 Probabilistic ICERs

2.1.2.1 Original base-case with revised PAS

The ICER is £34,790 per QALY gained in the probabilistic sensitivity analysis (with the revised PAS) using the original base-case assumptions.

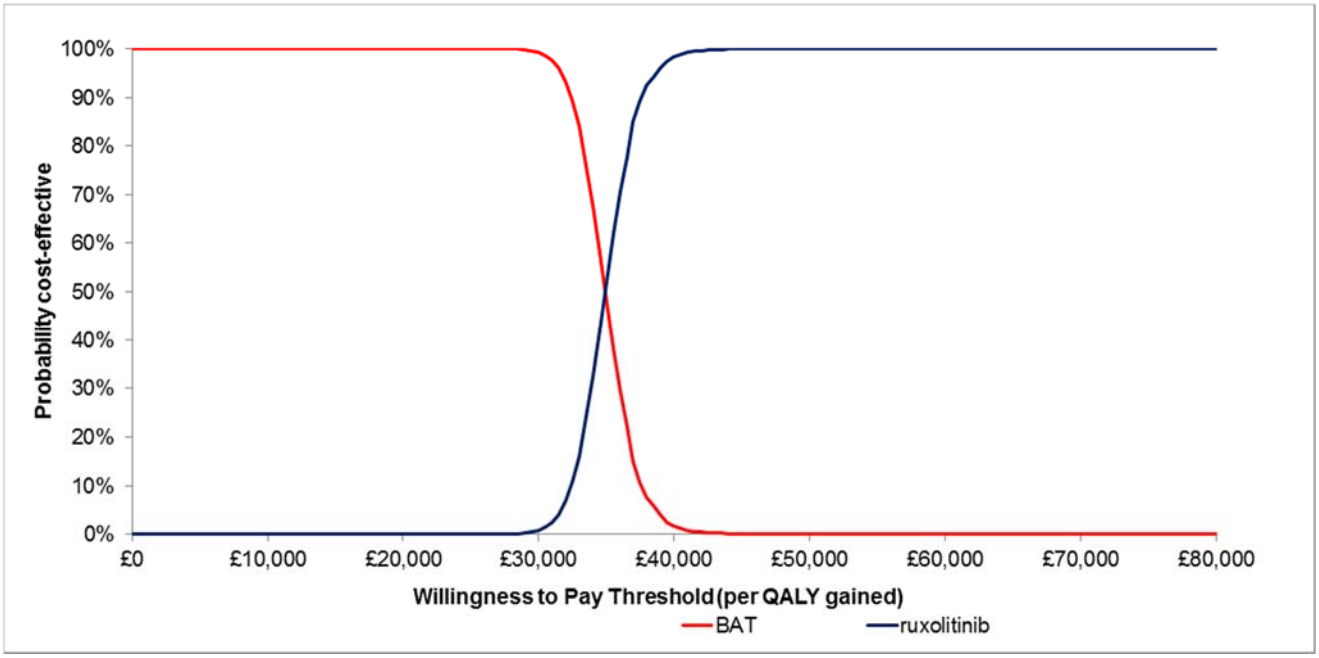
Table 3 Results of the probabilistic sensitivity analysis

	Life years (undiscounted)	QALYs (discounted)	Cost (discounted)	ICER
Ruxolitinib	6.06	4.02	£125,013	
BAT	2.15	1.47	£36,318	
Incremental	3.91	2.55	£88,696	**£34,790**

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

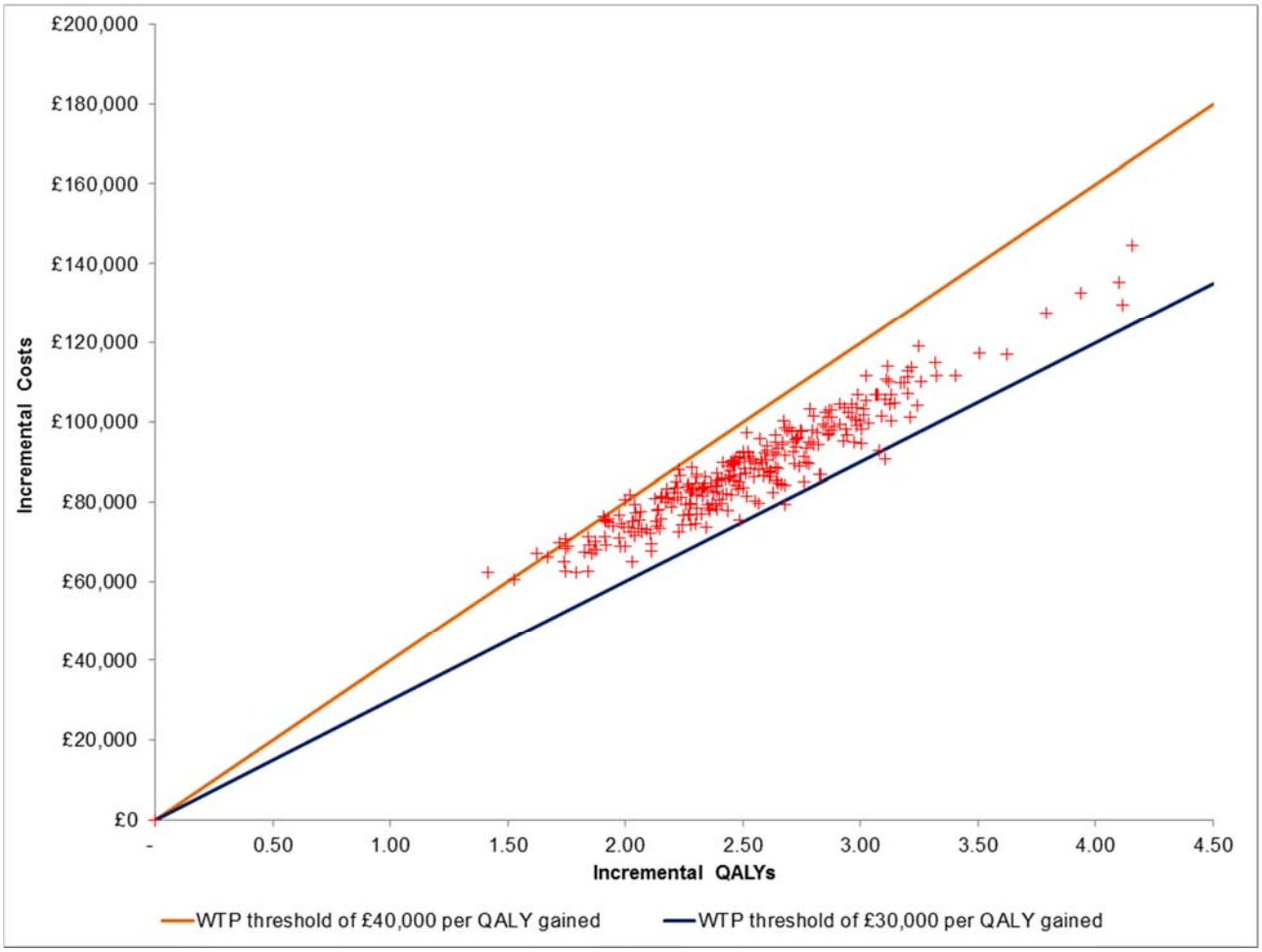
Figure 2 and Figure 3 show the cost effectiveness plane and cost effectiveness acceptability curve using results generated over a lifetime horizon. The curves show the probability of being cost effective for different levels that the decision maker may be willing to pay for an additional QALY. The cost effectiveness acceptability curves show that the probability of ruxolitinib being is a cost-effective strategy is 0.8%, 98.4% and 100% when using a threshold of £30,000, £40,000 and £50,000 per QALY gained, respectively.

Figure 2 Cost effectiveness acceptability curves



BAT, best available therapy; QALY, quality-adjusted life year.

Figure 3 Cost effectiveness plane



QALY, quality-adjusted life year. WTP, willingness to pay threshold

2.1.2.2 Revised base-case with revised PAS

The ICER is £31,240 per QALY gained in the probabilistic sensitivity analysis (with the revised PAS) using our revised base-case assumptions.

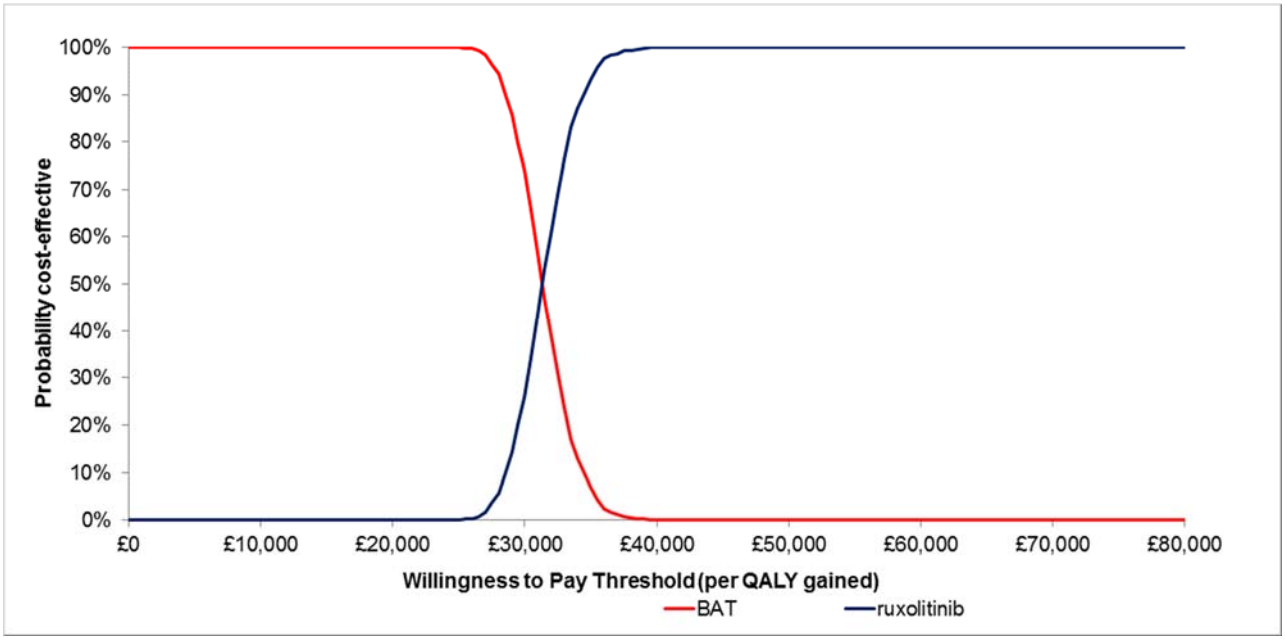
Table 4 Results of the probabilistic sensitivity analysis

	Life years (undiscounted)	QALYs (discounted)	Cost (discounted)	ICER
Ruxolitinib	6.07	4.49	£124,989	
BAT	2.16	1.63	£35,757	
Incremental	3.90	2.86	£89,232	**£31,240**

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

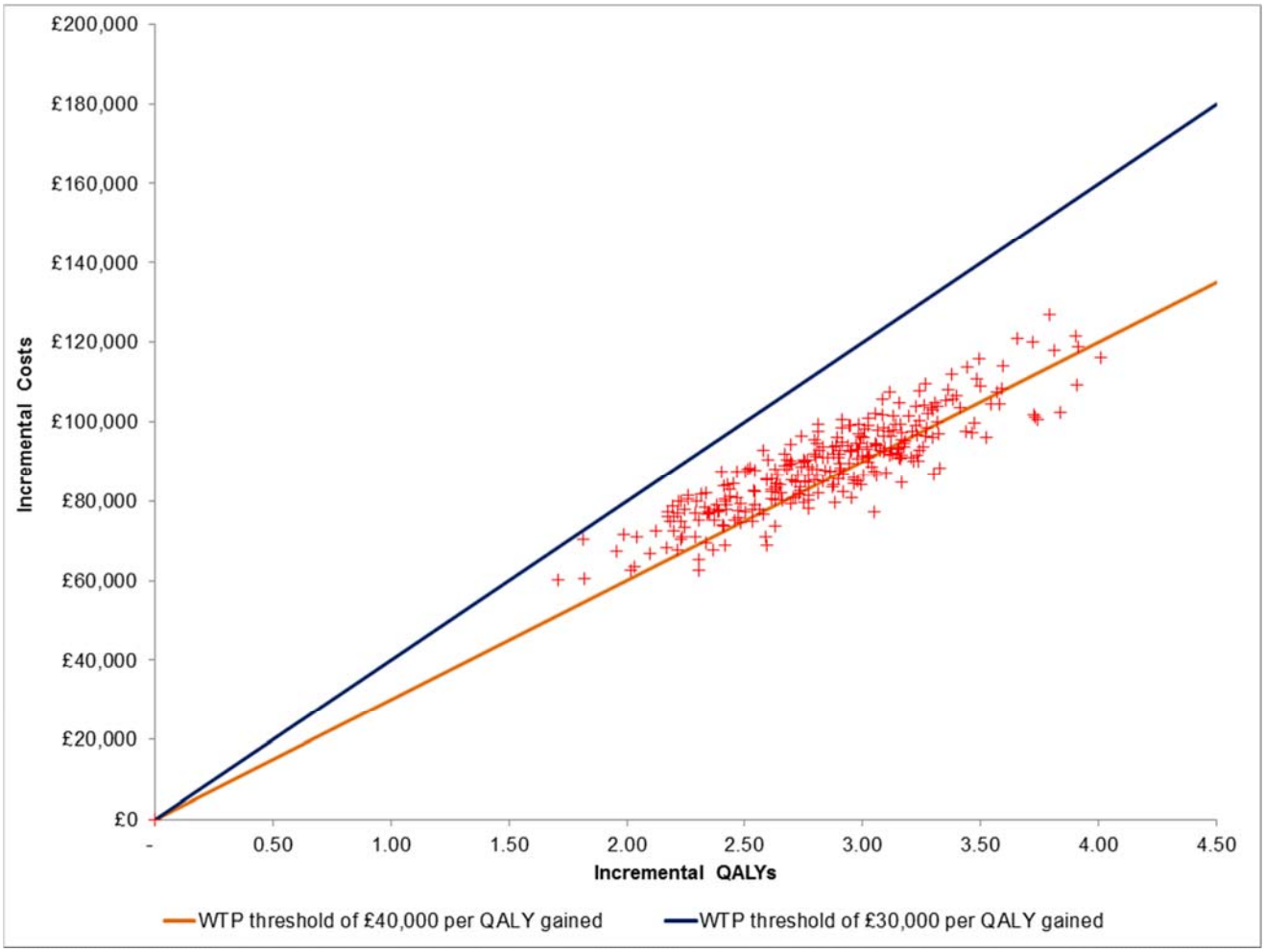
Figure 4 and Figure 5 show the cost effectiveness plane and cost effectiveness acceptability curve using results generated over a lifetime horizon. The curves show the probability of being cost effective for different levels that the decision maker may be willing to pay for an additional QALY. The cost effectiveness acceptability curves show that the probability of ruxolitinib being is a cost-effective strategy is 25.80%, 100% and 100% when using a threshold of £30,000, £40,000 and £50,000 per QALY gained, respectively.

Figure 4 Cost effectiveness acceptability curves



BAT, best available therapy; QALY, quality-adjusted life year.

Figure 5 Cost effectiveness plane



QALY, quality-adjusted life year. WTP, willingness to pay threshold

2.1.3 Sensitivity/scenario analyses

As highlighted by the ERG and accepted by the AC, the model was robust to variation in most input parameters and/or assumptions. Thus, for simplicity, sensitivity/scenario analyses are not presented here; but are presented in the PAS template.

3 Exploratory analysis (incorporing impact on quality of life of caregivers)

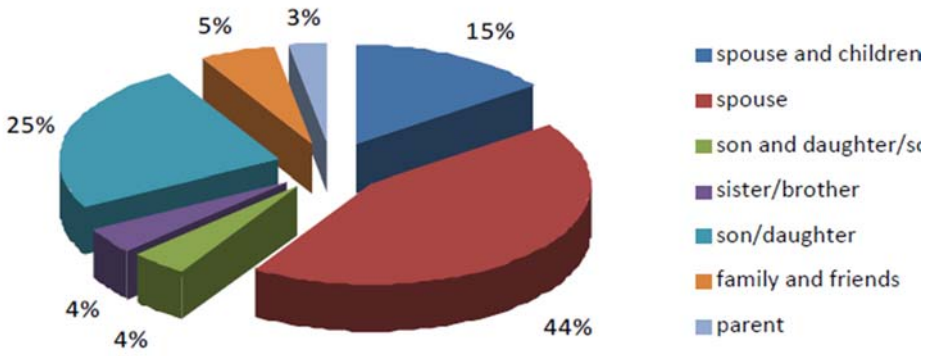
The NICE AC highlighted in Section 4.1 of the ACD that *"improving the symptoms associated with myelofibrosis, particularly fatigue and itching, would be greatly beneficial to the wellbeing of people with myelofibrosis and their families".* The NICE method guide also states that *"For the reference case, the perspective on outcomes should be all direct health effects, whether for patients or other people".*

As indicated in our original submission, MF is a rare and life-threatening disease which is characterised by a severe and progressive constellation of symptoms, including splenomegaly, night sweats, fever, weight loss, cachexia, pruritus, anaemia and fatigue.[4-6] Symptoms can be severely debilitating and have a major detrimental impact on a patient's HRQoL, and their ability to perform daily functions. The impact in terms of the deterioration in quality of life and diminished ability to perform daily functions is comparable to that observed in patients with metastatic cancer or acute myeloid leukaemia (AML).[5,7,8]

Studies have shown that, because of the extensive impact of MF on their daily life, patients with MF require a significant level of support from caregivers. A study conducted in Italy (Marini 2014)[9] indicated that 73 patients out of 127 (57.48%) interviewed had help from unpaid caregivers (both family and friends). This study included all MF patients and was not restricted to high and intermediate-2 patients. Patients with high and intermediate-2 are likely to require more help compared with patients with low and intermediate-1 risk. Therefore, we would expect more than 57.48% of intermediate-2/high risk patients to require caregiver assistance.

As illustrated in the figure below, the study also indicated that generally more than one caregiver was involved in order to guarantee the necessary help required by the patients. Therefore, the quality of life of more than one carer would be affected.

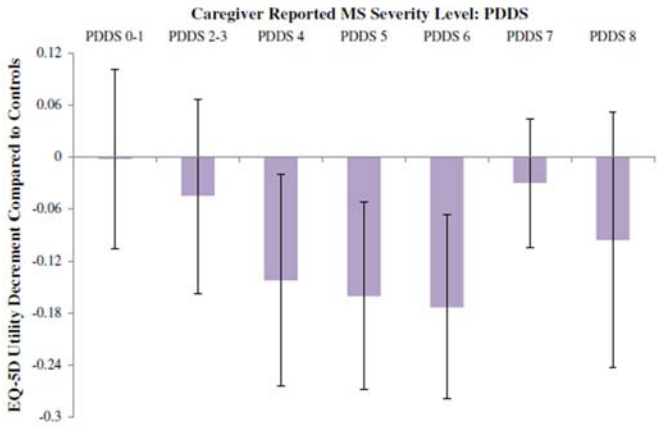
Figure 6 Caregiver group



There is a lack of evidence regarding the extent to which MF affects the quality of life of caregivers. However, studies in other disease areas provide some insights into the impact of various diseases on the quality of life of carers. A study carried out in France by Minaya Flores et al (2014)[10] showed that the decrement in utility for people who were caregivers for patients with glioma and other type of cancer (breast, lung, haematological, prostate, digestive, genital), compared with age-matched controls was about -0.10 as measured by the SF-6D.

A UK study (Acaster et al, 2013)[11] indicated that the utility decrement measured using the EQ-5D for caregivers of patients with multiple sclerosis could range from –0.002 to –0.173 depending on the severity of the patient's condition, when compared from a matched control sample from the UK general population. We note that the caregiving burden for multiple sclerosis is likely to be broadly similar to that for MF.

Figure 7 Utility decrement associated with caregiver compared to control by multiple sclerosis severity level



Reproduction of Figure 2 from Acaster et al, 2013[11] (error bars represent 1.96 x SE)

It should be noted that these studies provide an indication on the decrement in utility (not QALYs) compared to the norm.

In order to provide an indication of the ICER when the impact on caregiver's quality of life is included, an exploratory analysis is presented using the following assumptions:

a. An improvement in quality of life for caregiver is observed whilst on ruxolitinib
b. We assumed that 57.48% of patients require some help based on the Marini study.[9] As previously noted this is a conservative assumption as the study included all MF patients,
c. We assumed that, whilst on ruxolitinib, the quality of life of caregivers returns to that of the general population. This is likely to be optimistic (but the effect is attenuated by the first conservative assumption),
d. We assumed that, for each of the MF patients that needs care, the quality of life of 1.76 caregivers is affected. This is derived from Figure 6.

Using the revised PAS (discount of [redacted]%) and original base case assumptions, the ICER is £30,835 per QALY gained.

Table 5 Exploratory ICER under the revised PAS; original base-case assumption and inclusion of impact of MF of quality of life of caregivers

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
BAT	£36,238	1.476			
Ruxolitinib	£123,872	4.318	£87,633	2.84	£30,835

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; MF, myelofibrosis; PAS, Patient Access Scheme; QALY, quality-adjusted life years

Using the revised PAS (discount of [redacted]%) using the revised base-case assumptions, the ICER, is £28,111 per QALY gained.

Table 6 Exploratory ICER under the revised PAS; revised base-case assumption and inclusion of impact of MF of quality of life of caregivers

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
BAT	£35,422	1.628			
Ruxolitinib	£123,923	4.776	£88,502	3.15	£28,111

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; MF, myelofibrosis; PAS, Patient Access Scheme; QALY, quality-adjusted life years

While it is difficult to model explicitly the impact MF has on caregivers and families it is expected that only a small impact would be required for the ICER to fall below £30,000 per QALY gained.

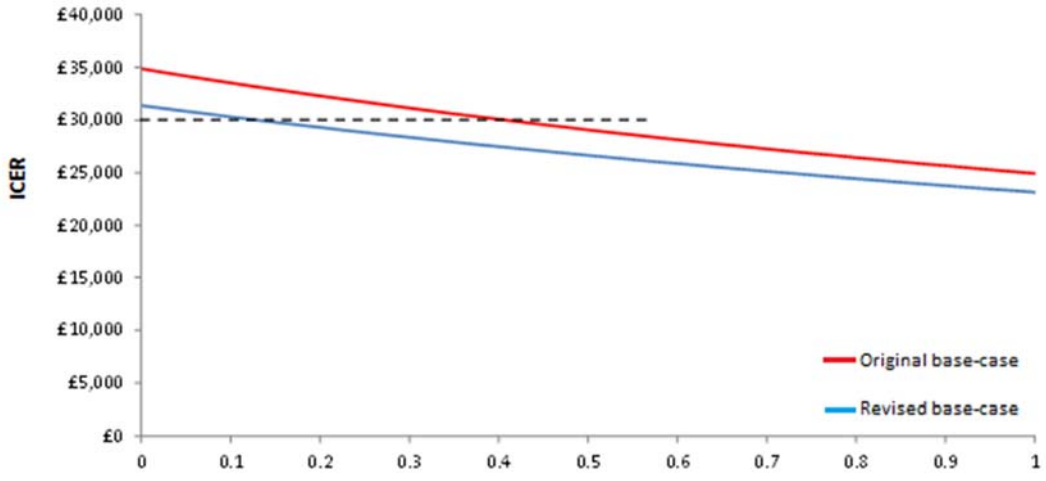
To illustrate this, a threshold analysis has also been presented to determine the level of discounted QALYs caregivers would need to gain over the lifetime to achieve a threshold of £30,000 per QALY gained with the introduction of ruxolitinib.

Results are presented using the revised PAS.

Under the original base case (£34,865), the number of discounted QALYs required to be gained from caregivers for the ICER to fall below a threshold of £30,000 per QALY gained is low at 0.41 QALYs over the lifetime (Figure 8).

Under the revised base case (£31,385) which corrected for errors/assumptions highlighted by the ERG, the number of discounted QALYs required to be gained from caregivers for the ICER to fall below a threshold of £30,000 per QALY gained is even lower at only 0.13 QALYs over the lifetime (Figure 8).

Figure 8 Threshold analysis – QALYs gained needed by the caregiver



Number of QALYs gained over the lifetime of a carer for an average patient

4 Additional considerations

4.1 Economic impact of MF on patients and carers

In addition to the impact on quality of life for caregivers, as highligted in our previous submission, the debilitating symptom burden, severe impact on quality of life and diminished ability to perform daily functions as a result of MF means than many patients are heavily reliant on informal carers and formal care via social services. The costs of family carer time and social services are likely to be considerable. Studies from Spain[12] and Italy[13] have shown that 3–11 hours per day of informal care are provided to MF patients. Based on the ONS estimate of £8.12 per hour,[14] the cost of providing informal care could amount to £8,900 to £32,000 per year. Between 18% and 28% of patients are medically disabled and these patients are likely to require formal care via social services.[15] Based on the median cost of a community care package for older people, the annual cost would amount to £19,000. When patients respond to ruxolitinib, with a resultant improvement in symptom burden and quality of life, it is expected that carer requirements will reduce significantly although we currently do not have the data to quantify such reductions.

These studies have also shown that MF can have a considerable economic impact on patients and their carers. A third of patients (35%) included in the study in Italy were unable to continue in employment, resulting in a mean loss of income of €8,065 per year.[13] Only 19% of caregivers managed to maintain their normal level of work hours, resulting in an average loss of quantifiable income of €4,692 per year. The small study in Spain estimated that costs

associated with work loss were €15,077 per patient.[12] While comparable information is not available for UK patients and carers, a similar loss of productivity is possible.

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Since the economic analysis does not include the impact on carers and social services nor the impact on productivity it is likely to underestimate the benefit of ruxolitinib in England and Wales.

4.2 Additional weighting due to end of life for the mixed population of patients with high and intermediate-2 risk MF

We believe that the survival for the mixed population of patients with high and intermediate-2 risk could be close to two years. Data from the UK Haematological Malignancy Research Network (HMRN) audit indicate that the median pooled survival from diagnosis for patients with high and intermediate-2 risk is 3.02 years (2.03–3.67). However, this survival is estimated from diagnosis and patients with MF are likely to initiate treatment at a later stage of the disease when survival will be shorter. Further, at this later disease stage, MF symptoms and splenomegaly require management.

4.3 Additional consideration when assessing the mixed population

The AC recognised that the population included in the economic model is composed of two clinically distinct groups: intermediate-2 and high risk MF and recognised that patients with high risk disease should be assessed againt the end-of-life threshold (typically around £50K) and patients with intermediate-2 against the typical NICE threshold. The AC also considered the ICER to be applicable to both high and intermediate-2 MF patients.

The high risk group represents a significant proportion of the two combined sub-groups: in the COMFORT-II trial the proportions were 60% high risk and 40% intermediate-2 risk while clinical experts in England estimate that the high risk group comprises 50% of the total of the intermediate-2 plus high risk MF group of patients. The HMRN audit also shows a similar split with 48% of patients being high-risk (and 52%, intermediate-2 risk). These data from the HMRN region are considered representative of the whole of the UK.[16]

As the base case ICER is based on the full population from the COMFORT-II trial which include a mixed population of high and intermediate-2 risk MF patients, it is reasonable to assume that the cost-effectiveness threshold for ruxolitinib (for the mixed population from which the ICER is derived) should be assessed against a higher threshold than the typical £30,000 per QALY gained threshold, The AC accepted that approximately half of the population has a threshold in the region of £50k and the combined population, therefore, should have a combined threshold between 30K and £50k.

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CONFIDENTIAL UNTIL PUBLISHED

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

ERG commentary on the additional information submitted by the company in response to the ACD

Produced by **CRD and CHE Technology Assessment Group, University of York, Heslington, York YO10 5DD**

Date **27/11/2015**

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined.

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1 Introduction

The evidence review group (ERG) was requested by NICE to provide validity checks on the additional evidence submitted by the company in response to the appraisal consultation document (ACD) and to identify any areas of remaining uncertainty. Due to the limited time available, the additional work undertaken by the ERG does not constitute a formal critique of the company's resubmission and hence does not accord with the procedures and templates applied to the original submission. However, the ERG has checked the implementation of any proposed changes and ensured replication of the results presented by the company. In addition, the ERG has also undertaken additional scenario analysis to address any remaining issues or areas of uncertainty that it considered was not reflected in the company's response.

The company's response to the ACD included:

A. Revised base case
    a. A revised patient access scheme (PAS);
    b. Correction of the errors identified by the ERG on formula for the inclusion of Leukaemic transformation (LT) (section 5.2.10.1 of the ERG report);
    c. Adjusting baseline utility by a factor of 10%;
    d. Assuming responders spend time on best available therapy (BAT) after ruxolitinib discontinuation;
    e. Exclusion of lenalidomide;
B. Exploratory analysis (incorporating impact on quality of life of caregivers).

The ERG considers that the documentation submitted in the company's resubmission (CrS) largely reflects amendments and corrections intended to address the committee's considerations raised within the ACD and ERG report.

2 Revised base case

In this section, the ERG presents the following:

- A critique of company's revised base-case;
- Results of company's original base-case with revised PAS;
- Results of Comapny's revised base-case with revised PAS;
- Scenario analysis to show impact of alternative base-line utility adjustment and alternative proportion of time responders spend on BAT after ruxolitinib discontinuation.

2.1 Critique on Company's revised base-case

The company has proposed a revised PAS which is now incorporated into a revised base-case which includes a number of significant changes to the model presented in the original CS. The revised PAS and changes to the base case model are detailed below.

2.1.1 Revised Patient Access Scheme

In the revised PAS, ruxolitinib is now priced at [redacted] per pack (5mg) and [redacted] per pack (10, 15 & 20 mg); a discount of [redacted] compared to the published list price. Table 1 shows the published list price per pack, price with the previous PAS and price with the current PAS. The ERG has checked the revised economic model and can confirm that the revised PAS has been correctly implemented by the company.

Table 1 Price of Ruxolitinib with and without PAS

	Cost per 56-tablet blister pack (excluding VAT)		
	List price	With PAS (previous submission)	With PAS (current submission)
5 mg	£1,680	[redacted]	[redacted]
10 mg	£3,360	[redacted]	[redacted]
15 mg	£3,360	[redacted]	[redacted]
20 mg	£3,360	[redacted]	[redacted]

2.1.2 Correction of the errors identified by the ERG on formula for the inclusion of LT

In the current submission, the errors identified by the ERG on the formulas in previous company submission for the inclusion of the LT are amended as per ERG suggested code. The ERG has checked the revised economic model and can confirm that these have been correctly implemented by the company.

2.1.3 Adjusting baseline utility by a factor of 10%

The original company submission (CS) drew utility values from COMFORT-I. As note in the original CS and CrS the patients enrolled in COMFORT –I had to be "resistant or refractory to, intolerant of, or, in the investigators opinion, not candidates for available therapy." This restrictive criterion for enrolment implies that the patients enrolled in the COMFORT-I have potentially more severe disease and lower quality of life than those enrolled in COMFORT-II (which placed no such restriction on enrolment) and more importantly more severe disease than the patients likely to receive ruxolitinib therapy in practice. As consequence of this in the original CS a scenario analysis was presented in

which baseline utility values were inflated by 5%. Noting the issues highlighted above, the ERG in their critique suggested that this scenario may represent a more realistic estimate of the ICER for ruxolitinib (see Section 5.2.1.6, ERG report).

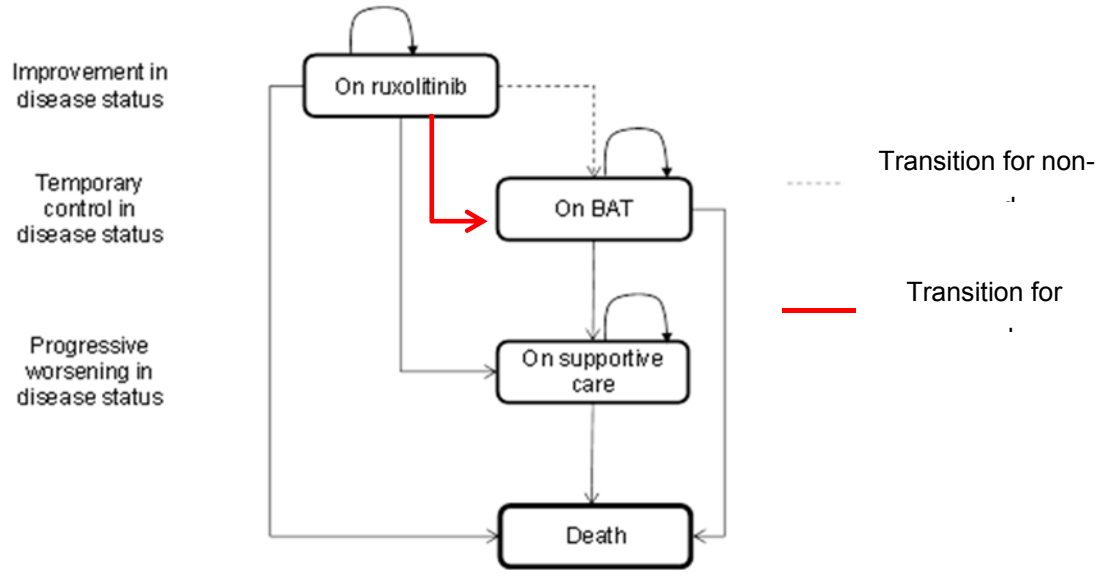
In response to this observation by the ERG, the company's revised base case adjusts the baseline quality of life, inflating it by a factor of 10%. The value of 10% was justified on the basis of clinical opinion suggesting that this could appropriately represent the baseline utility of patients enrolled in COMFORT-II. The ERG accepts that such an inflation factor may be appropriate and may represent a more realistic estimate of the ICER. However, the ERG does have some concerns regarding the magnitude of inflation factor, which is based solely on clinical opinion and was not considered by the company to be a plausible scenario in the original submission. Given the limited evidence to support this assumption, there is substantial uncertainty regarding the magnitude of the inflation factor and the ERG considers the unadjusted values and a 5% inflation to be as plausible as the 10% value presented in company's new base case. The ERG has therefore conducted a scenario analysis using an adjusting factor of 5%.

2.1.4 Assuming responders spend time on BAT after ruxolitinib discontinuation

In the ERG report, it was highlighted that the transition of treatment responders directly to supportive care may not be representative of clinical practice and at least a proportion of these patients are likely to go on to receive BAT therapy.

In the CrS, it is therefore assumed that responders would spend a proportion of their time post-ruxolitinib on BAT before moving to supportive care, as depicted in Figure 1 (red line).

Figure 1 Updated simplified schematic of the model structure



BAT, best available therapy.

Patients initiating BAT when not previously exposed to ruxolitinib remain in the model approximately 45% of their time alive on BAT (based on the COMFORT-II trial). In the revised model the company therefore assumed that responders on ruxolitinib would spend 30% of their time alive post cessation of ruxolitinib on BAT. No other data were available to inform the proportion of responders time spend on BAT.

The consequences of this change to the model structure are that the decline in utility patients are assumed to experience on supportive care is delayed for patients receiving ruxolitinib resulting in more QALYs accruing to ruxolitinib patients. These additional QALYs are however, set against additional drug costs from providing BAT.

The ERG acknowledge that in practice it is likely that a proportion of patients will transit to BAT therapy rather than directly to supportive care, but have a number of concerns regarding how the company has attempt to represent this in the revised base case.

Firstly, the 30% value chose by the company is almost entirely arbitrary and there is minimal evidence to justify the company's suggestion that this is a conservative assumption it may well be optimistic we just don't know. Secondly, the ERG's comment implies that a proportion of patient may receive BAT whilst the revised base case assumes that all patients will receive BAT therapy for a period of time. No supporting evidence is provided to justify the fact the all patients will go on to receive BAT following cessation of ruxolitinib. It is the ERG's opinion that it is far from certain that this reflects clinical practice. Thirdly, the model assumes that BAT will be as effective for patients who have exhausted ruxolitinib as those who initiate on BAT and therefore will experience similar quality of life (QoL). This seems far from obvious, there is clear potential for these patients to have lower QoL than those who initiate on BAT. For these reasons this revised structure is subject to substantial uncertainty and indeed may lead to an underestimation of the ICER due to an overestimation of the utility gains. The ERG therefore presents a scenario analysis to illustrate the impact of company's assumption on the ICER.

2.1.5 Exclusion of lenalidomide

In the previous submission, the ERG questioned the inclusion of lenalidomide in the BAT basket of therapies. During the clarification response, the ERG requested an analysis in which patients receiving lenalidomide would receive hydroxyurea instead and it was included in the ERG's preferred base-case. The CrS considers that it is unlikely that patients receiving lenalidomide would instead receive hydroxyurea. The assumption made is based on The British Committee for Standards in Haematology (BCSH) guidelines[1]. In the company's revised base case, lenalidomide is therefore replaced with thalidomide which is more in line with UK guidelines. This alternative assumption has minimal impact on the resulting ICER and is plausible as the original assumption presented in the ERG's base case.

2.2 Results of CS's Original base-case with revised PAS

In this section, the results of the original company base case are presented with the revised PAS (discount of [redacted]). The results show that, over a lifetime, for patients initiating treatment on ruxolitinib, the discounted incremental QALYs are 2.55 and discounted incremental costs are £88,728 compared to BAT in the probabilistic analysis (Table 2). The ICER for ruxolitinib therapy is £34,789 per QALY gained in the probabilistic analysis (Table 2). The CrS also presents the deterministic analysis results which are similar to the results from the probabilistic analysis.

Table 2 CS's original base-case with revised PAS

	Life years (undiscounted)	QALYs (discounted)	Cost (discounted)	ICER
Ruxolitinib	6.09	4.03	£125,427	
BAT	2.16	1.48	£36,700	
Incremental	3.93	2.55	£88,728	£34,789

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

2.3 Company's revised base-case with revised PAS

The CrS makes a number of alterations to the company's original base case as outlined in section 2.1. The results of this analysis are presented in Table 3. The model predicted that, over a lifetime, for patients initiating treatment on ruxolitinib discounted incremental QALYs are 2.858 and discounted incremental costs are £89,248 compared to BAT in the probabilistic analysis. The ICER for ruxolitinib therapy is £31,229 per QALY gained in the probabilistic analysis. The CrS also presents results of deterministic analysis which is similar with the results from the probabilistic analysis. (Table 3)

Table 3 Results of the probabilistic sensitivity analysis of CS's revised base-case with revised PAS (results of probabilistic analysis)

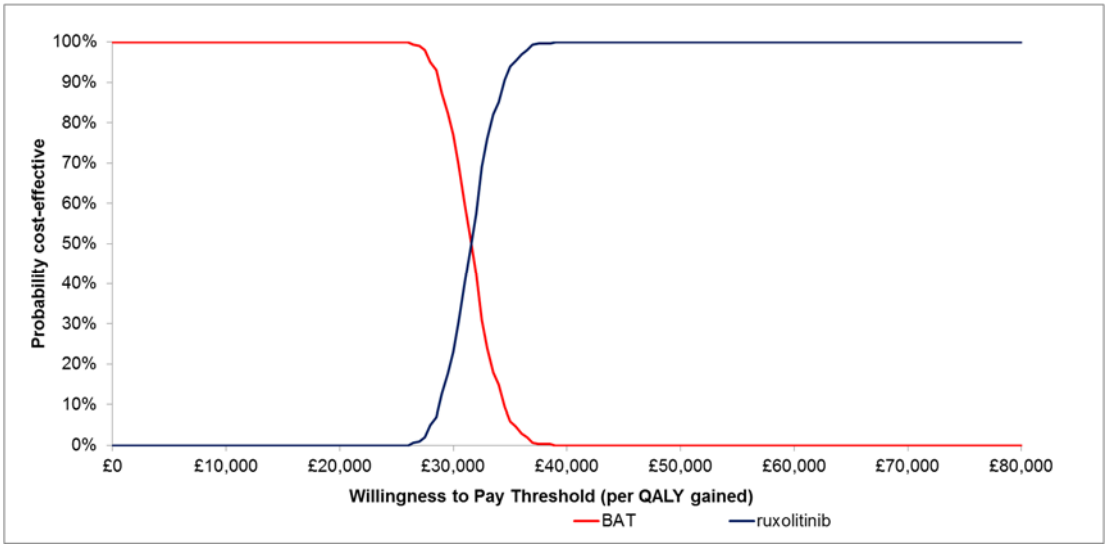
Technologies	Life years (undiscounted)	QALYs (discounted)	Cost (discounted)	ICER
Ruxolitinib	6.08	4.492	£124,970	
BAT	2.17	1.634	£35,722	
Incremental	3.91	2.858	£89,248	£31,229

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

Figure 2 and Figure 3 show the cost effectiveness plane and cost effectiveness acceptability curve using results generated over a lifetime horizon. The curves show the probability of being cost effective for different levels that the decision maker may be willing to pay for an additional QALY.

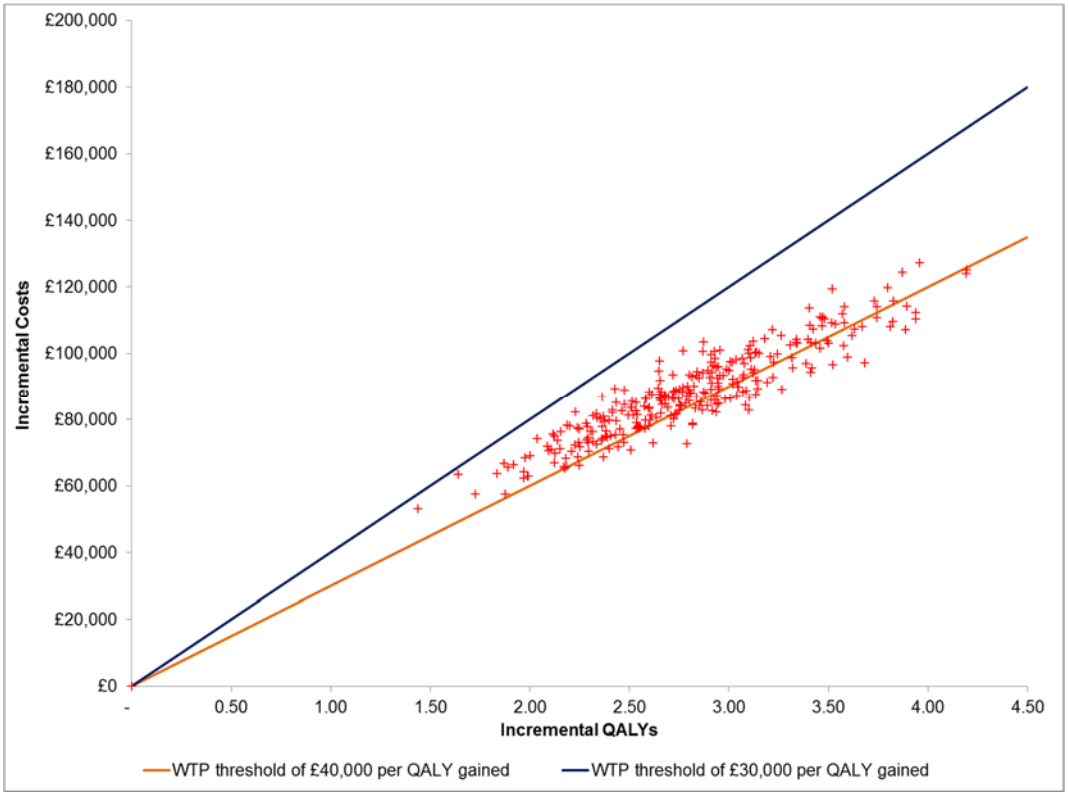
The cost effectiveness acceptability curves show that the probability of ruxolitinib being is a cost-effective strategy is 25.80%, 100% and 100% when using a threshold of £30,000, £40,000 and £50,000 per QALY gained, respectively.

Figure 2 Cost effectiveness acceptability curves of CS's revised base-case with revised PAS



BAT, best available therapy; QALY, quality-adjusted life year.

Figure 3 Cost effectiveness plane of CS's revised base-case with revised PAS



QALY, quality-adjusted life year. WTP, willingness to pay threshold.

2.4 Scenario analysis

Detailed sensitivity/scenario analyses were not presented in the CrS. However, these scenario analyses were present in the PAS template. In this report, the ERG has conducted the following scenario analyses in detail:

- Alternative base-line utility adjustment
- Alternative proportion of time responders spend on BAT after ruxolitinib discontinuation

2.4.1 Alternative base line utility adjustment

In the company's revised base-case, the base-line utility is inflated using adjusting factor of 10%. Scenario analyses are conducted assuming no adjustment for base-line utility and adjustment factor of 5% (Table 4).

Table 4 Scenario analysis: Alternative base-line utility adjustment vs. CS's revised base-case (results of probabilistic analysis)

	RUXOLITINIB		**BAT**		**ICER**
	QALYs (discounted)	**Costs (discounted)**	**QALYs (discounted)**	**Costs (discounted)**	
CS's revised base case (10% adjustment for base line utility)	**4.49**	**£124,970**	**1.63**	**£35,722**	**£31,229**
5% adjustment for base-line utility	4.31	£125,360	1.55	£35,664	£32,545
no adjustment for base-line utility	4.14	£125,939	1.48	£35,784	£33,899

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

2.4.2 Alternative proportion of time responders spend on BAT after ruxolitinib discontinuation

In the company's revised base-case, it is assumed that the responders on ruxolitinib spend 30% of their time alive post cessation of ruxolitinib on BAT. Scenario analyses are conducted assuming the responder will no spend time on BAT therapy, 10% and 20% of time on BAT therapy (Table 5).

Table 5 Scenario analysis: Alternative proportion of time responders spend on BAT after ruxolitinib discontinuation vs. CS's revised base-case (results of probabilistic analysis)

	RUXOLITINIB		BAT		
	QALYs (discounted)	Costs (discounted)	QALYs (discounted)	Costs (discounted)	ICER
CS's revised base-case (30% of time spent on BAT therapy)	**4.49**	**£124,970**	**1.63**	**£35,722**	**£31,229**
20% of time spent on BAT therapy	4.49	£125,384	1.64	£35,486	£31,488
10% of time spent on BAT therapy	4.43	£124,793	1.63	£35,603	£31,827
no time spent on BAT therapy	4.45	£125,727	1.64	£35,625	£32,081

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

3 ERG's preferred base-case

In the previous ERG report, the ERG presented a preferred base-case making the following changes to the original company base-case: adding in drug wastage in ruxolitinib at a rate of 5%; removing lenalidomide from the basket of therapies that make up BAT; assuming that time on ruxolitinib is part of the period of time on treatment on BAT for non-responders; assuming that the BAT discontinuation rate is underestimated by 20%; and assuming 7.06% mortality rates for ruxolitinib responders. (Section 6.5, ERG report)

Incorporating the revised PAS (discount of [redacted]) to the ERG's original preferred base-case, the ICER for ruxolitinib therapy is £37,722 per QALY gained in the probabilistic analysis (Table 6). The probability of ruxolitinib being cost-effective at £30,000, £40,000 and £50,000 per QALY gained is cost effectiveness acceptability curves show that the probability of ruxolitinib being is a cost-effective strategy is 0%, 81.90% and 100% respectively.

Table 6 Results of probabilistic analysis of ERG's original preferred base-case with revised PAS

	Life years (undiscounted)	QALYs (discounted)	Cost (discounted)	ICER
Ruxolitinib	5.90	3.93	£128,403	
BAT	2.16	1.49	£36,095	
Incremental	3.74	2.45	£92,308	£37,722

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

Considering the comments from committee and the revised base case, we present a revised base case to which the revised PAS (discount of [redacted]) is applied. This ERG revised base case acknowledges the uncertainty regarding estimating drug wastage and therefore assumes no drug wastage, we also make the more optimistic assumption of 0% mortality while on ruxolitinib as assumed in the company's base case. The revised base-case however makes two amendments to the company's revised base, specifically:

- Time on ruxolitinib is assumed to be part of the period of time on treatment on BAT for non-responders;
- BAT discontinuation rate is underestimated by 20%.

Given the uncertainty regards to some the amendments presented in the company's revised model we present two alternative scenarios. In the first scenario we assume no adjustment to baseline utility is made and assume that patients discontinuing ruxolitinib treatment move directly to supportive care as per the original CS. In the second scenario we assume baseline utility is inflated by 10% and that patients discontinuing ruxolitinib therapy spend 30% of their remaining time alive on BAT as per the revised company model. Table 7 presents the results of the probabilistic analysis for these two scenarios. The ICER for ruxolitinib therapy under scenario one is £35,632 per QALY gained. The ICER for ruxolitinib therapy under scenario two is £31,676 per QALY gained. The ERG considers these two scenarios to be as plausible as one another and to be at least as plausible as the revised base case presented by the company.

Table 7 Results of probabilistic analysis of ERG's revised preferred base-case with revised PAS

Technologies	Incremental life years (undiscounted)	Incremental QALYs (discounted)	Incremental Cost (discounted)	ICER
Scenario 1	3.84	2.49	£88,619	£35,632
Scenario 2	3.85	2.81	£88,971	£31,676

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

The cost effectiveness acceptability curves show that the probability of ruxolitinib being is a cost-effective strategy under scenario one is 0.33%, 94.33% and 100% when using a threshold of £30,000, £40,000 and £50,000 per QALY gained. Under scenario two the cost effectiveness acceptability curves show that the probability of ruxolitinib being is a cost-effective strategy 21.67%, 100% and 100% when using a threshold of £30,000, £40,000 and £50,000 per QALY gained.

4 Exploratory analysis (incorporating impact on quality of life of caregivers)

In the current submission, an exploratory analysis was presented incorporating the potential impact of MF on the quality of life of caregivers. The company justify this analysis on the basis that the NICE methods guide states that *"For the reference case, the perspective on outcomes should be all direct health effects, whether for patients or other people"*. On this basis the company explain that the debilitating impact of MF on patients means that many will require care from family and friends and that this burden should potentially be considered when evaluating the impact of ruxolitinib therapy.

The company note the lack of evidence regarding the extent to which MF affects the quality of life of caregivers, but cite two studies suggesting a quality of life impact upon carers. The first is a French study (Flores et al[2]) which showed that the decrement in utility for caregivers of patients with glioma and other types of cancer (breast, lung, haematological, prostate, digestive, genital), compared with age-matched controls. This analysis showed a decrement of utility of approximately 0.10 as measured by the SF-6D. The second study (Acaster et al[3]) was a UK study that indicated the utility decrement measured using the EQ-5D for caregivers of patients with multiple sclerosis could range from –0.002 to –0.173 depending on the severity of the patient's condition, when compared from a matched control sample from the UK general population[3]. The CrS notes that the caregiving burden for multiple sclerosis is likely to be broadly similar to that for MF.

The CrS goes on to present an exploratory analysis incorporating the impact on quality of life on carers. This analysis makes the following assumptions:

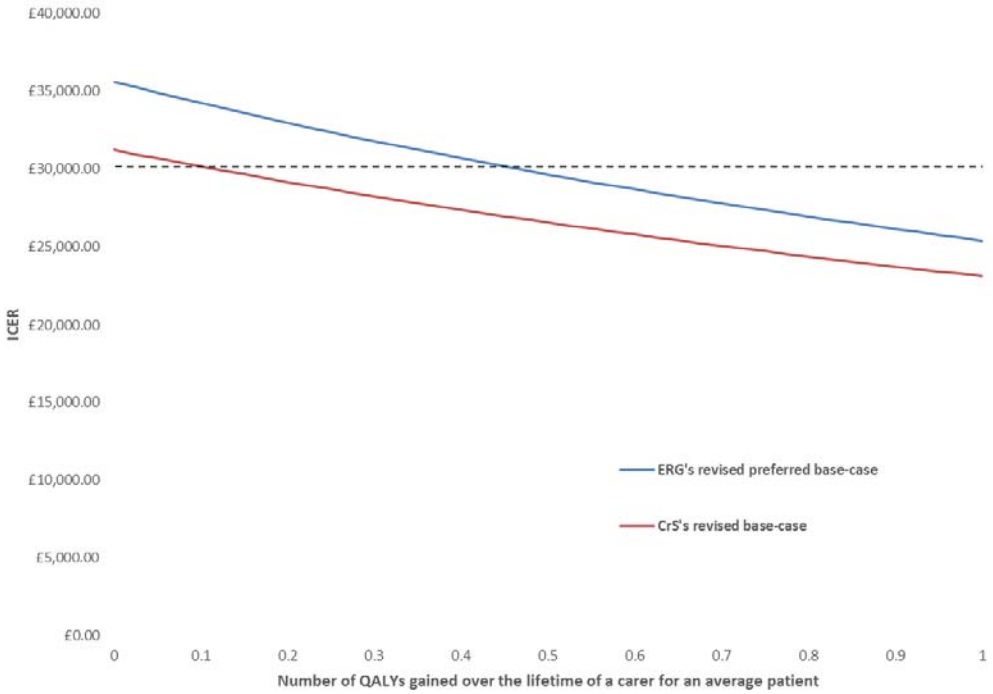
- That 57.48% of patients require some help based on the Marini study.[4]
- That carers of MF patients on BAT experience a 0.1 decrement to their utility based on the Flores study;
- That whilst on ruxolitinib, the quality of life of caregivers returns to that of the general population;
- That for each of the MF patients that needs care, the quality of life of 1.76 caregivers is affected. This is derived from the Marini study[4].

Using the CrS's revised base-case and incorporating impact of quality of life of the caregivers, the ICER is £28,060 per QALY gain. In contrast, incorporating the impact on quality of life of the caregivers into the ERG's most pessimistic base case (Scenario one) in which no inflation in utility values are assumed and in which patients discontinuing ruxolitinib therapy are assumed to move directly to supportive care gives an ICER of £31,855 per QALY gained.

The CrS also includes a threshold analysis to determine the level of discounted QALYs caregivers would need to gain over the lifetime to achieve a threshold of £30,000 per QALY gained with the introduction of ruxolitinib. (Section 4, pg. 16-17, CS response to ACD)

Under the CrS's revised base-case (£31,229), the number of discounted QALYs required to be gained from caregivers for the ICER to fall below a threshold of £30,000 per QALY gained is 0.117 QALYs over the lifetime (Figure 6). However, under the most pessimistic base case (Scenario one, £35,632), the number of discounted QALYs required to be gained from caregivers for the ICER to fall below a threshold of £30,000 per QALY gained is much higher at 0.462 QALYs over the lifetime (Figure 7).

Figure 4 Threshold analysis – QALYs gained needed by the caregiver



The ERG has a number of concerns regarding the assumptions and data used in this analysis. Firstly, the use of non-UK data to estimate the prevalence of carers may not be representative of UK population, particular as Italy has very different culture with regards to caring for family members. Secondly the data on which the decrements in utility are estimated are from quite different disease areas and may not be extrapolable to carers of MF patients. Furthermore, the two studies provide only limited support for proposition that the health of caregivers is adversely affected. The Flores et al[2] study does not find a statistically significant decrease in SF-6D and therefore the cited 0.1decrement is a statistically insignificant difference, while, the study by Acaster et al[3] show only statistical significant differences for some multiple sclerosis patients. Finally, the assumption that the quality of life of care givers returns to that of the general population whilst on ruxolitinib is overly optimistic and is likely to lead to an underestimate of the ICER. To some extent this final issue is addressed by the threshold analysis, but the threshold analysis is difficult to interpret as it is based on lifetime QALY gains rather than changes to the utility decrement. Given these issues the impact on quality of life of caregivers estimated by the company on ICER needs to be considered cautiously and is subject to substantial uncertainty.

5 Additional ERG comments

5.1 Economic impact of MF on patients and carers

In the original CS, it was highlighted that there is potential impact of ruxolitinib on carer costs and impact on productivity and it is again highlighted in this CrS. However, carer costs and costs of

productivity loss are not included in the NICE reference case. Therefore, the ERG have not evaluated the potential economic impact of MF on patients and carers.

5.2 End of life

In both the original CS and the CrS the company states that the survival for the mixed population of patients with high and intermediate-2 risk could be close to two years. The CrS presents data from the UK Haematological Malignancy Research Network (HMRN) audit[5] to justifying this position. This reports that the median survival from diagnosis for patients with intermediate-2 and high risk are 3.12 years (1.88 – 4.60) and 2.80 years (1.47 – 3.67), and the median pooled survival from diagnosis for patients with high and intermediate-2 risk is 3.02 years (2.03–3.67). None of these risk groups meet the end of life criteria set by NICE, of normally less than 24 months. However, the CrS goes on to argue that these estimates of survival are estimated from diagnosis and patients with MF are likely to initiate treatment at a later stage of the disease when survival will be shorter. The ERG consider this a possibility, however the ERG notes that the median survival of patients in the BAT group from the COMFORT–II trial (who may be considered representative of the patients eligible for ruxolitinib therapy) was 28 months (mean 26 months), exceeding the 24 month threshold.

6 ERG summary of company's response

As previously highlighted the ERG considers that the documentation submitted in the CrS largely reflects the amendments and corrections intended to address the committee's considerations and points raised in the ERG report. The revised model submitted by the company primarily implements a revised PAS and makes a number of changes to the model. Additionally, an exploratory analysis with new data is presented to show the impact on the quality of life for caregivers.

The ERG considers that the company has appropriately altered the model to reflect the changes documented in the company's response to the ACD. However, the ERG has a number if concerns regarding a number of these changes and the assumptions upon which they are based. These relate to:

- **Inflation of baseline utility by 10%:** This assumption is not supported by any data, but instead clinical opinion. The ERG acknowledges that some inflation may be appropriate and that there is the limited evidence to suggest an appropriate inflation factor. However, the ERG are concerned about the plausibility of the magnitude of the presented inflation factor and note this was not considered a plausible scenario in the original CS. The adjustment of the baseline utility has a large impact on the ICER.
- **Responders on ruxolitinib spend 30% of their time alive post ruxolitinib cessation on BAT:** The ERG acknowledges that the original assumption that of patients discontinuing ruxolitinib therapy moved directly to supportive care was potential a conservative one. However, the ERG has a number of concerns regards the changes to this assumption

implemented in the company's revised model. Specifically, the ERG note that this 30% rate is almost entirely arbitrary and based on minimal data. Furthermore, it far from certain that all patients will transit to BAT and it is far more likely that only a proportion will. This is not reflected in this new assumption. This change to the model also makes the optimistic assumption that patients on BAT following ruxolitinib therapy will have the same QoL as those initiating on BAT. There is therefore significant potential that this new assumption is overly optimistic and underestimating the ICER.

- **Exploratory analysis incorporating the caregivers' quality of life:** The incorporation of care givers' quality of life within the economic analysis has relatively large impact on the ICER. The ERG notes the limited data available to inform this analysis, but concerned about the quality of the evidence used to justify this analysis particularly due to the fact that the QoL losses are observed in a different disease area. The ERG therefore consider this analysis subject to significant uncertainty and should be interpreted cautiously.

The ERG carried out scenario analyses based a revised version of the company's revised model a presenting two scenarios. The first assumes no inflation to base line utility and that patients move directly to supportive care. The second assumes a 10% inflation base line utility and that 30% of patients time post cessation of ruxolitinib is spent on BAT. The ICERs for the analyses are £35,632 and £31,676 respectively per QALY gained. The ERG considers the ICERs from these two scenarios to be at least as plausible as the ICER presented in the CrS of £31,229.

7 References

1. Reilly JT, McMullin MF, Beer PA, Butt N, Conneally E, Duncombe A, et al. Guideline for the diagnosis and management of myelofibrosis. *Br J Haematol* 2012;**158**:453-71. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22651893

2. Minaya Flores P, Berbis J, Chinot O, Auquier P. Assessing the quality of life among caregivers of patients with gliomas. *Neuro-oncology practice* 2014;**1**:191-7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26034632

3. Acaster S, Perard R, Chauhan D, Lloyd AJ. A forgotten aspect of the NICE reference case: an observational study of the health related quality of life impact on caregivers of people with multiple sclerosis. *BMC Health Serv Res* 2013;**13**:346. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24016141

4. Marini AG CA, Abruzzese E et al. Back to life project. Living, treating and managing myelofibrosis. The burden of illness for the patients and their families. *Unpublished report by the ISTUD Foundation* 2014.

5. Haematological Malignancy Research Network. Myelofibrosis Audit. Clinical management, resource utilisation and outcome in primary and secondary myelofibrosis; Last updated: 02 October 2012.

Sent by email:

Dear Nan,

As you know, we are preparing for the 2nd Committee meeting discussion for this topic on 13 January, and the ERG are reviewing the ACD comments and Novartis' new evidence (including the updated PAS and cost-effectiveness analyses for the full high risk and Intermediate-2 patient population) at this time.

In order for the Committee to be best placed to make their decisions at the meeting, NICE request that you provide more cost-effectiveness analyses to include ICER's for the intermediate – 2 risk patients and the high-risk patients separately, both including the updated PAS discount. This is in line with NICE's expectation from our earlier advice regarding Novartis proposed approach to this new evidence request (see email trail below).

Please can you confirm receipt and your ability to provide the updated analyses by **5pm Tuesday 5 January.**

Thanks in advance for your consideration,

Kind regards,

Frances

Dr Frances Sutcliffe
Associate Director Technology Appraisals - Committee C
National Institute for Health and Care Excellence
Level 1A | City Tower | Piccadilly Plaza | Manchester M1 4BT | United Kingdom

Single Technology Appraisal (STA)

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

Request from 21 December 2015: NICE request that you provide more cost-effectiveness analyses to include ICER's for the intermediate-2 risk patients and the high-risk patients separately, both including the updated PAS discount.

Response

In response to this request, exploratory analyses have been conducted separating patients with high and intermediate-2 IPSS risk myelofibrosis (MF). In brief, the Excel economic model submitted to NICE on 17 November 2015 in response to the Appraisal Consultation Document was amended to use separate data for high and intermediate-2 IPSS risk for the following inputs:

- Overall survival (OS) for best available therapy (BAT) adjusted for cross-over (using the rank-preserving structural failure time method),
- response group whilst on ruxolitinib,
- probability of discontinuation for responders on ruxolitinib,
- survival post-ruxolitinib discontinuation,
- the dosage received,
- change in health-related quality of life (HRQoL),
- number of outpatient visits for patients receiving BAT.

Novartis considers that these analyses should be viewed as **exploratory only**, given the small number of patients available to derive separate inputs for high and intermediate-2 IPSS risk groups of patients. The sample size reduces further as inputs are separated by responders and non-responders (Table 1). The small sample size reduces the confidence in the extrapolation of the survival curves and may lead to inconsistencies. The results presented for the separate analyses of patients with high and intermediate-2 IPSS risk are therefore not considered reliable and should be viewed with a high degree of caution.

Table 1: Number of patients and events available for survival analysis

	Intermediate-2 IPSS		High IPSS	
	Number of patients	Number of Events	Number of patients	Number of Events
OS for BAT adjusted for cross-over	[redacted]	[redacted]	[redacted]	[redacted]
Probability of discontinuation for responders (spleen only) on ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]
Survival post-ruxolitinib discontinuation in both spleen responders and early discontinuers	[redacted]	[redacted]	[redacted]	[redacted]

In the pivotal COMFORT clinical trials, the proportions of patient enrolment by risk classification were approximately 40% intermediate-2 risk and 60% high risk. In UK clinical practice, is it estimated that the overall intermediate-2/high risk group comprises 50% intermediate-2 and 50% high risk patients. This is based on the HMRN audit where, of the two combined subgroups, 52% were intermediate-2 and 48% high risk. Expert clinical opinion confirms that the split is 50:50. The Appraisal Committee has agreed that the high risk patients treated with ruxolitinib meet the end of life criteria and are deemed cost-effective under the original PAS.

Results

Results are presented for three groups separately: the overall trial population (combined intermediate-2 and high risk), intermediate-2 and high risk patients. Similar to the approach used in our response to the ACD, for completeness, we report results using (a) the original base case with revised patient access scheme (PAS), (b) the revised base case using revised assumptions and (c) exploratory analyses including the impact on caregiver HRQoL.

1. Original base case with revised PAS

1.1. Combined group

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Increment-al QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
BAT	£36,238	2.15	1.476				£24,553	
RUXOLITINIB	£123,872	5.96	3.989	£87,633	3.81	2.51	£31,050	£34,865

1.2. Intermediate-2 risk IPSS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incre-mental LYG	Incre-mental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
BAT	£36,277	2.14	1.512				£23,990	
RUXOLITINIB	£159,565	9.20	5.881	£123,288	7.06	4.37	£27,132	£28,220

1.3. High risk IPSS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
BAT	£36,122	2.15	1.439				£25,107	
RUXOLITINIB	£94,517	4.08	2.819	£58,395	1.93	1.38	£33,524	£42,295

2. Revised base case with revised PAS

The original base case shown above was revised in our response to the ACD in order to account for (a) errors identified by the ERG on the inclusion of leukaemic transformation (LT) in the economic model, (b) adjusting the baseline utility, (c) change to the treatment pathways for responders to ruxolitinib and (d) the exclusion of lenalidomide. Results for this revised base case, split by risk classification, are presented below.

2.1. Combined group

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
BAT	£35,422	2.15	1.628				£21,758	
RUXOLITINIB	£123,923	5.96	4.448	£88,502	3.81	2.82	£27,862	£31,385

2.2. Intermediate-2 risk IPSS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
BAT	£35,336	2.14	1.664				£21,239	
RUXOLITINIB	£159,765	9.20	6.469	£124,429	7.06	4.80	£24,698	£25,896

2.3. High risk IPSS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
BAT	£35,411	2.15	1.591				£22,263	
RUXOLITINIB	£94,530	4.08	3.147	£59,119	1.93	1.56	£30,039	£37,985

3. **Exploratory analysis (revised base case, revised PAS and incorporating impact on caregivers' quality of life)**

Studies have shown that, because of the extensive impact of MF on their daily life, patients with MF require a significant level of support from caregivers. Evidence from other disease areas provides some insights into the impact of various diseases on the quality of life of these carers. Drawing on this information, an exploratory analysis was presented in our response to the ACD to illustrate that, under a series of assumptions regarding the impact of MF on caregiver quality of life, the ICER would be reduced. Results for this exploratory analysis, split by risk classification, are presented below.

3.1. Combined group

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
BAT	£35,422	2.15	1.628				£21,758	
RUXOLITINIB	£123,923	5.96	4.776	£88,502	3.81	3.15	£25,946	£28,111

3.2. Intermediate-2 risk IPSS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
BAT	£35,336	2.14	1.664				£21,239	
RUXOLITINIB	£159,765	9.20	6.917	£124,429	7.06	5.25	£23,099	£23,688

3.3. High risk IPSS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
BAT	£35,411	2.15	1.591				£22,263	
RUXOLITINIB	£94,530	4.08	3.370	£59,119	1.93	1.78	£28,053	£33,229

CONFIDENTIAL UNTIL PUBLISHED

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

ERG commentary on the additional information submitted at the request OF NICE

Produced by	**CRD and CHE Technology Assessment Group, University of York, Heslington, York YO10 5DD**
Date	**11/01/2016**

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined.

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1 Introduction

The evidence review group (ERG) was requested by National Institute for Health and Care Excellence (NICE) to provide validity checks on the additional evidence submitted by the company at the request of NICE that the economic analysis be carried out for two subgroups namely intermediate-2 and high risk patients . Due to the limited time available, the additional work undertaken by the ERG does not constitute a formal critique of the company's resubmission and hence does not accord with the procedures and templates applied to the original submission. The ERG has however, been able to carry out a check of the implementation of the documented changes and ensured replication of the results presented by the company. No addition scenario analyses were carried out by the ERG as part of this critique.

The company's response to the NICE request for further analysis included two new base case analyses for intermediate-2 and high risk patients. The ERG considers the documentation submitted in the this additional submission to reflect NICE's requested analysis, but provides only a limited documentation of the additional analysis carried out and the resulting changes made to the model. As such, the ERG is able to provide only limited commentary on the additional analysis carried out and its impact on the resulting incremental cost effectiveness ratio (ICER).

2 Critique on Company's Implementation of sub group analysis

The implementation of the subgroup analysis appears to have been appropriately implemented. The ERG however, noted two issues.

Firstly, the revised model assumes that the proportion of patients dying while on best available therapy (BAT) does not change with the subgroup. There is likely to be a small difference in the observed number of deaths across the two groups that occurred while on BAT. This difference is, however, unlikely to have a significant impact on the estimated ICER.

Secondly the probabilistic sensitivity analysis (PSA) did not function for the subgroup analyses. This problem occurs due to zero observed events for a number of inputs, consequently leading to issues with estimating the confidence intervals. The ERG was not able to rectify these issues and run the PSA in the limited time available to the ERG to assess the model. Previous iterations of the model have, however, shown that the deterministic and probabilistic results to be similar. It is therefore reasonable to assume this would be case for the subgroup analysis, though this is not entirely certain given the added uncertain present in these subgroup analyses.

3 Results of additional subgroup analysis

The results of the subgroup analysis were presented for the original base case, a revised base case presented in the company's response to the appraisal consultation document (ACD) and an additional exploratory analysis including carers' quality of life. All three sets of results included a revised patient access scheme (PAS) present in the company's response to the ACD. The results of these three sets of analysis are presented in Table 1, Table 2 and Table 3 respectively. In all three sets of results the ICER is significantly lower for the Intermediate -2 risk group than the high risk group. In all three scenarios the ICER for the Intermediate -2 risk group was less than £30,000 per quality adjusted life year (QALY), while the ICER for the high risk group exceed £30,000 per QALY in all cases, but was less than the £50,000 per QALY.

Table 1: Original base case with revised PAS

	Incremental Life years (undiscounted)	**Incremental QALYs (discounted)**	**Incremental Cost (discounted)**	**ICER**
Combined group	**3.81**	**2.51**	**£87,633**	**£34,865**
Intermediate-2 risk	7.06	4.37	£123,288	£28,220
High risk	1.93	1.38	£58,395	£42,295

Table 2: Revised base case with revised PAS

	Incremental Life years (undiscounted)	**Incremental QALYs (discounted)**	**Incremental Cost (discounted)**	**ICER**
Combined group	**3.81**	**2.82**	**£88,502**	**£31,385**
Intermediate-2 risk	7.06	4.80	£124,429	£25,896
High risk	1.93	1.56	£59,119	£37,985

Table 3: Exploratory analysis (revised base case, revised PAS and incorporating impact on caregivers' quality of life)

	Incremental Life years (undiscounted)	**Incremental QALYs (discounted)**	**Incremental Cost (discounted)**	**ICER**
Combined group	**3.81**	**3.15**	**£88,502**	**£28,111**
Intermediate-2 risk	7.06	5.25	£124,429	£23,688
High risk	1.93	1.78	£59,119	£33,229

4 Interpretation and reliability of results

The analysis presented by the company shows significant differences in the magnitude of the estimated ICER for the two subgroups. These differences cannot be attributed to difference in any singular input, but originate from a combination of factors. Firstly, the subgroup analysis shows substantial differences in the response and prognosis of patients receiving ruxolitinib in the two risk groups. Specifically, there are substantial differences in both the rate of response and overall survival (OS) of patients on ruxolitinib between the two groups. These differences are summarised Table 4. Secondly these significant differences in the prognosis of patients receiving ruxolitinib are juxtaposed against minimal differences in prognosis for patients receiving BAT (Table 4). This combination of large differences across subgroups for ruxolitinib patients and small differences for BAT patients is the primary reason for the observed difference in the estimated ICERs.

Table 4: Summary of differences in response and prognosis

	Ruxolitinib			**BAT**		
	Combined group	**Intermediate-2 risk**	**High risk**	**Combined group**	**Intermediate-2 risk**	**High risk**
Duration on ruxolitinib	179.72	258.96	115.91	-	-	-
Duration on BAT	39.35	67.77	27.57	48.27	55.72	42.03
Duration on supportive care	90.83	151.85	68.57	63.74	55.78	69.86
Total time alive	309.90	478.58	212.06	112.01	111.50	111.89
Proportion of LT	8.70%	12.74%	6.48%	6.00%	5.98%	5.88%
Proportion of responders	61.57%	65.81%	51.19%	-	-	-

The company noted that these analyses should be considered exploratory and caution against interpreting the results of this analysis at face value. The ERG wishes to reiterate this point and considers these subgroup analyses subject to significant uncertainty. The ERG would particularly draw attention to the lack of any difference in OS between the intermediate-2 risk and high risk patients. This lack of any difference in OS across subgroups is inconsistent with external data reported in Haematological Malignancy Research Network (HMRN) audit[1, 2] which show substantial differences in OS between these two risk groups.

5 References

1. Cervantes F, Dupriez B, Pereira A, Passamonti F, Reilly JT, Morra E, et al. New prognostic scoring system for primary myelofibrosis based on a study of the International Working Group for Myelofibrosis Research and Treatment. *Blood* 2009;**113**:2895-901.

2. Passamonti F, Cervantes F, Vannucchi AM, Morra E, Rumi E, Pereira A, et al. A dynamic prognostic model to predict survival in primary myelofibrosis: a study by the IWG-MRT (International Working Group for Myeloproliferative Neoplasms Research and Treatment). *Blood* 2010;**115**:1703–8.