

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

Technology appraisal guidance

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Your responsibility

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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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This guidance replaces TA289.

1 Recommendations

- 1.1 Ruxolitinib is recommended as an option for treating disease-related splenomegaly or symptoms in 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, and
 - if the company provides ruxolitinib with the discount agreed in the patient access scheme.
- 1.2 People whose treatment with ruxolitinib is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

2 The technology

- 2.1 Ruxolitinib (Jakavi, Novartis) is a protein kinase inhibitor that targets Janus-associated kinase (JAK) signalling. Ruxolitinib has a UK marketing authorisation for 'the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis'. It is administered orally. The recommended starting dose is 15 mg twice daily for patients with a platelet count between 100,000/mm³ and 200,000/mm³, and 20 mg twice daily for patients with a platelet count of more than 200,000/mm³. The maximum recommended starting dose for patients with platelet counts between 50,000/mm³ and 100,000/mm³ is 5 mg twice daily.
- 2.2 The summary of product characteristics lists the following adverse reactions for ruxolitinib: anaemia, thrombocytopenia, neutropenia, bleeding and weight gain. For full details of adverse reactions and contraindications, see the summary of product characteristics.
- 2.3 The cost of ruxolitinib is £3,360 for a 56-tablet pack of 10 mg, 15 mg or 20 mg tablets, or £1,680 for a 56-tablet pack of 5 mg tablets (British national formulary [BNF], December 2015). This amounts to an annual cost of about £43,680 per patient (assuming a 15 mg or 20 mg dose, taken twice daily, for 52 weeks). The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of ruxolitinib with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 Evidence

The appraisal committee ([section 7](#)) considered evidence submitted by Novartis and a review of this submission by the evidence review group (ERG; [section 8](#)). See the [committee papers](#) for full details of the evidence.

Clinical effectiveness

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

Overview of the randomised controlled trials

3.2 COMFORT-I is a multicentre (USA, Canada and Australia), phase III, randomised, double-blinded trial that compared ruxolitinib (15 mg or 20 mg twice daily, n=155) with placebo (n=154) in people with primary myelofibrosis (45.2% of ruxolitinib group; 54.5% of placebo group), or myelofibrosis secondary to polycythaemia vera (32.3% of ruxolitinib group; 30.5% of placebo group) or essential thrombocytopenia (22.6% of ruxolitinib group; 14.3% of placebo group). Patients who enrolled on the trial had resistant or refractory myelofibrosis, or available therapy was contraindicated or not tolerated. All patients on the trial had intermediate-2 risk or high-risk myelofibrosis, a platelet count of at least 100×10^9 /litre and a palpable spleen length of at least 5 cm. The duration of the study was 24 weeks, after which patients could enter an open-label extension phase. In COMFORT-I, patients were eligible to crossover to ruxolitinib treatment. Before week 24, patients on placebo needed to have symptom worsening and 25% or more spleen volume increase from baseline. After week 24, patients needed to have 25% or more spleen volume increase from baseline.

3.3 COMFORT-II is a multicentre (Europe, including sites in the UK), phase III, randomised, open-label trial that compared ruxolitinib (15 mg or 20 mg twice

daily, n=146) with best available therapy (n=73) in people with primary myelofibrosis (53% of ruxolitinib group; 53% of the best available therapy group), or myelofibrosis secondary to polycythaemia vera (33% of ruxolitinib group; 27% of best available therapy group) or essential thrombocythaemia (14% of ruxolitinib group; 19% of best available therapy group). Best available therapy comprised a range of treatments. The most frequently used were hydroxycarbamide, prednisolone and epoetin alfa. Other treatments used as best available therapy included lenalidomide and thalidomide. All patients on the trial had intermediate-2 or high-risk myelofibrosis, a platelet count of at least 100×10^9 /litre and a palpable spleen length of at least 5 cm. The company stated that the trial population may have been healthier than the general population with myelofibrosis because the trial excluded people with uncontrolled hypertension, unstable angina and a life expectancy of less than 6 months. The duration of the trial was 48 weeks, after which patients could enter an open-label extension phase. In COMFORT-II, patients were eligible to crossover to ruxolitinib treatment. Patients on best available therapy whose disease progressed (defined according to the study protocol as either 25% or more increase in spleen volume from on-study nadir, including baseline, or needing splenectomy, splenic irradiation or leukaemic transformation) could crossover to have ruxolitinib at any time.

- 3.4 The primary outcome for both COMFORT-I and COMFORT-II was the proportion of patients achieving a spleen volume reduction of 35% or more from baseline, assessed by MRI or CT scan. The primary efficacy outcome was measured at 24 weeks in COMFORT-I and at 48 weeks in COMFORT-II.
- 3.5 Secondary outcomes for the COMFORT-I trial included maintenance of reduction in spleen volume, reduction in palpable spleen length, change in total symptom score (measured using the modified myelofibrosis symptom assessment form [MF-SAF] v2.0 diary), overall survival, and health-related quality-of-life measures. Secondary outcomes for the COMFORT-II trial included outcomes from the COMFORT-I trial, as well as the time to achieve a spleen volume reduction of 35% or more, progression-free survival, leukaemia-free survival and transfusion dependency. In COMFORT-II, additional overall survival analyses were carried out at 3.5 years follow-up.
- 3.6 The intention-to-treat (ITT) population was used for all efficacy end points. Patients who stopped treatment or crossed over before 24 weeks (in

COMFORT-I), or did not have a 48-week assessment of spleen volume (in COMFORT-II because of discontinuation and entering the open-label extension phase) were counted as patients whose disease did not respond (for change in spleen volume and symptom score).

- 3.7 In COMFORT-I, a statistically significantly greater proportion of patients in the ruxolitinib group achieved a reduction in spleen volume of 35% or more from baseline, compared with the placebo group at 24 weeks (41.9% versus 0.7%; $p < 0.001$). In COMFORT-II, a statistically significantly greater proportion of patients in the ruxolitinib group achieved a reduction in spleen volume of 35% or more from baseline, compared with the best available care group at 48 weeks (28% versus 0%; $p < 0.001$). In COMFORT-I, a statistically significantly greater proportion of patients in the ruxolitinib group achieved a reduction in total symptom score of 50% or more from baseline, compared with the placebo group at week 24 (45.9% versus 5.3%; $p < 0.001$). This outcome was not collected in COMFORT-II.
- 3.8 Overall survival was a secondary end point in both COMFORT trials and neither was designed to be sufficiently powered to detect a statistically significant difference in overall survival between treatment groups.
- 3.9 In COMFORT-I, overall survival was statistically significantly improved with ruxolitinib over placebo at a median follow-up of 51 weeks; 91.6% compared with 84.4% (hazard ratio [HR] 0.50; 95% confidence interval [CI] 0.25 to 0.98) and 102 weeks (HR 0.58; 95% CI 0.36 to 0.95). At a median follow-up of 3 years, 42 patients in the ruxolitinib group and 54 patients in the placebo group had died and the difference in overall survival was no longer statistically significant (HR 0.69; 95% CI 0.46 to 1.03). Because crossover was permitted during the treatment period of the study the company provided an analysis that adjusted for crossover using the rank preserving structural failure time (RPSFT) method. Ruxolitinib was associated with a 64% reduction in the risk of death compared with placebo (HR 0.36; 95% CI 0.20 to 1.04).
- 3.10 In COMFORT-II, overall survival was not statistically significantly different between ruxolitinib and best available therapy at a median follow-up of 61 weeks. It reached borderline statistical significance at a median of 112 weeks of follow-up: 86% compared with 78% (HR 0.52; 95% CI 0.27 to 1.00). At median follow-up of 3 years, 20% (29 patients) in the ruxolitinib group and 30%

(22 patients) in the best available therapy group had died, and ruxolitinib was associated with a 52% reduction in the risk of death compared with best available therapy (HR 0.48; 95% CI 0.28 to 0.85). The probability of survival at 144 weeks was 81% in the ruxolitinib group and 61% in the best available therapy group.

- 3.11 The company provided the results of a further analysis done at median follow-up of 3.5 years, which included additional survival information for 15 of 41 patients who were previously deemed lost to follow-up. At 3.5 years of follow-up, 27% (40 patients) in the ruxolitinib group and 40% (30 patients) in the best available therapy group had died. Ruxolitinib was associated with a 42% reduction in the risk of death compared with best available therapy (HR 0.58; 95% CI 0.36 to 0.93); median overall survival had not yet been reached. The probability of survival at 3.5 years was 71% in the ruxolitinib group and 54% in the best available therapy group (p=0.02).
- 3.12 The company was asked during the clarification stage to provide an overall survival analysis with adjustment for crossover using the RPSFT method for the COMFORT-II trial. 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 is confidential and is therefore not presented here).
- 3.13 Because median overall survival was not reached in the ruxolitinib group, it was not possible to directly calculate the median (or mean) survival benefit associated with ruxolitinib compared with best available therapy, and therefore estimated values needed to be modelled. The company included a summary of an indirect comparison made between the ruxolitinib treatment group of COMFORT-II and the Dynamic International Prognostic Scoring System (DIPSS) cohort. The DIPSS database is a multicentre database and includes 519 people with primary myelofibrosis, who were not having any experimental drug or haematopoietic stem cell transplantation. Matched patients (n=350) were compared with patients with primary myelofibrosis enrolled in COMFORT-II (n=100). The number of observed deaths in the 2 cohorts was 30 (30%) on ruxolitinib and 256 (86%) on best available therapy, generating estimates of median survival of 5 years from diagnosis (95% CI 2.9 to 7.8) on ruxolitinib compared with 3.5 years (95% CI 3.0 to 3.9) for the DIPSS cohort.
- 3.14 Adverse event data were collected in COMFORT-I at 24 weeks and at 48 weeks

in COMFORT-II. Anaemia was the most common grade 3 or 4 adverse event in COMFORT-I (45%) and COMFORT-II (42%). In COMFORT-II, the most common adverse event was diarrhoea, and it was more frequently reported with ruxolitinib compared with best available therapy (23% compared with 12%). There were more grade 3 or 4 adverse events with ruxolitinib than with best available therapy (42% compared with 25%). There was a similar number of people with grade 3 or 4 thrombocytopenia with ruxolitinib compared with best available therapy (8% compared with 7%). Treatment was stopped in 12 people (8.2%) in the ruxolitinib group and 4 people (5.5%) in the best available therapy group because of adverse events.

- 3.15 Although symptom reduction was not specifically assessed in the COMFORT-II trial, the company carried out a post hoc exploratory analysis of health-related quality of life and symptom analyses on the primary analysis data set (at 48 weeks) from COMFORT-II. Of the 9 symptom scores assessed by the Global Health Status (EORTC QLQ-C30), 6 symptom scores (appetite loss, dyspnoea, fatigue, insomnia, pain and diarrhoea) were improved with ruxolitinib compared with best available therapy.
- 3.16 Health-related quality of life was assessed in the COMFORT trials using the Global Health Status (EORTC QLQ-C30) and Functional Assessment of Cancer Therapy for patients with Lymphoma (FACT-Lym) questionnaires. There were statistically significant gains in favour of ruxolitinib in the average change in health-related quality of life in the COMFORT-I trial, and there were improvements in all health-related quality-of-life subscales in favour of ruxolitinib in the COMFORT-II trial.

Overview of the non-randomised controlled studies

- 3.17 The ROBUST study was a phase II study that was done in the UK (n=48). It included patients with intermediate-1, intermediate-2 and high-risk disease. At week 48, 40% of patients achieved reduction in spleen length of at least 50% and 21% achieved a reduction in total symptom score of at least 50% (as assessed using MF-SAF). Treatment success, defined as a 50% or more decrease in spleen length and/or total symptom score at week 48, was achieved by 50.0% of the overall population and 57.1%, 38.5% and 52.4% of the intermediate-1 risk, intermediate-2 risk and high-risk disease groups respectively. Consistent with findings from the COMFORT trials, the most common haematological

adverse events were anaemia (45.8% of patients) and thrombocytopenia (37.5%).

- 3.18 The phase III expanded-access, Janus-associated kinase (JAK)-inhibitor ruxolitinib in myelofibrosis patients (JUMP) trial was also designed to assess the safety and efficacy of ruxolitinib in patients with high-risk, intermediate-2 risk or intermediate-1 risk disease. As of September 2014, 2138 patients had been enrolled in 25 countries and data had been reported for an analysis of 1144 patients who had ruxolitinib for a median of 11.1 months. At week 48, 61% of patients achieved at least a 50% reduction from baseline in palpable spleen length. Clinically meaningful improvements in symptoms, as assessed using the FACT-Lym total score, were seen as early as week 4 and were maintained during the study. Ruxolitinib was generally well-tolerated, with only 14% of patients stopping treatment as a result of adverse events. The most common grade 3 or 4 haematological adverse events were anaemia (33.0%), thrombocytopenia (12.5%) and neutropenia (3.9%); each of these rarely led to discontinuation of ruxolitinib. The incidences of grade 3 or 4 non-haematological adverse events were low.
- 3.19 The JUMP study included patients with low platelet counts (at least 50 to under 100×10^9 /litre). In this patient population, ruxolitinib was started at a dose of 5 mg twice daily. This could be increased to 10 mg twice daily at week 4 in patients whose disease had not responded adequately, if platelet counts were at least 50×10^9 /litre and there had been no treatment-related toxicities that resulted in dose reduction, interruption or discontinuation during initial treatment. Results of an interim analysis for 6 months of therapy in the first 50 patients with low platelet counts were reported. At this time point, 82% of patients (31 of 38 patients starting therapy on 5 mg twice daily) remained on the 5 mg twice daily dose and 18% had a dose escalation to 10 mg twice daily. At week 24, 38.2% (13 of 34 evaluable patients) achieved a reduction of at least 50% from baseline in palpable spleen length; overall, 44.7% of patients (21/47) achieved at least a 50% reduction from baseline in spleen length at any time. Clinically meaningful improvements in symptoms, as assessed using the FACT-Lym total score, were seen as early as week 4 (mean change from baseline, 8.2) and were still seen at week 12 (change from baseline, 9.6). However, the reduction in splenomegaly and improvements in symptoms seen in this subgroup of patients were not as good as those achieved for the overall JUMP population. The adverse effect profile was consistent with previous studies in

patients with platelet counts under 100×10^9 /litre. The most common grade 3 or 4 haematological adverse events were thrombocytopenia (30%) and anaemia (28%): 3 patients (6%) stopped treatment because of thrombocytopenia and 1 patient stopped because of anaemia. Grade 1 or 2 haemorrhages were reported in 4 (8%) patients and grade 3 or 4 haemorrhages in 2 (4%) patients. Rates of grade 3 or 4 non-haematological adverse events were low. Nine patients (18%) stopped therapy because of adverse events. The company commented that this analysis suggested that ruxolitinib doses of 5 to 10 mg twice daily were generally well tolerated and efficacious in patients with myelofibrosis who have platelet counts of at least 50 to under 100×10^9 /litre.

3.20 Study 258 was a phase II dose-finding study investigating the efficacy and safety of ruxolitinib in patients with low platelet counts (50 to 100×10^9 /litre). Patients were started on a dose of 5 mg twice daily, with the option to increase to 10 mg twice daily if platelet counts remained adequate. An interim analysis of data from this study reported that by week 24, 62% of patients achieved stable doses of at least 10 mg twice daily. A median percentage reduction in spleen volume of 24.2% was achieved and 20% of patients achieved a reduction in spleen volume of at least 35.0% at 24 weeks. When evaluated by titrated dose (average dose over the last 4 weeks of the study, up to week 24), median percentage reductions from baseline in spleen volume at week 24 were 16.7% for patients who had 5 mg once or twice daily ($n=7$), and 28.5% for patients who had 10 mg twice daily ($n=20$). Decreases in total symptom score were also seen in patients who completed 24 weeks of therapy ($n=32$). The median percentage reduction from baseline in total symptom score for patients who completed 24 weeks of therapy was 43.8%. The study reported a mean change in Global Health Status (EORTC QLQ-C30) score from baseline of approximately 13 at week 24.

3.21 Thrombocytopenia was the most frequently reported grade 3 or 4 adverse event, occurring in 56% of patients. Grade 3 or 4 anaemia was reported in 42% of patients. Most other adverse events were grade 1 or 2 and no other grade 3 or 4 adverse events were reported in more than 2 (4%) of patients. Thrombocytopenia that needed dose reductions and dose interruptions occurred in 12 (24%) and 8 (16%) of patients respectively, and occurred mainly in patients with baseline platelet counts of 75×10^9 /litre or less. Two patients stopped treatment as a result of adverse events: in 1 patient, this was because of grade 4 thrombocytopenia; and the reason was not reported for the other patient. The company stated that the results of this study indicated ruxolitinib,

started at a dose of 5 mg twice daily, can benefit patients with low platelet counts.

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

Cost effectiveness

- 3.23 The company submitted an individual patient discrete event simulation model comparing ruxolitinib with best available care. The company considered this design to be more flexible and transparent compared with a Markov cohort approach. The model had a lifetime horizon of 35 years. Although the model did not use time cycles, it effectively had a cycle length of 1 week, because this was the shortest unit of time in the model. The company based the analysis on an NHS and personal social services perspective, and costs and benefits were discounted at an annual rate of 3.5%. There were 4 health states in the model: on ruxolitinib, on best available therapy, on supportive care and death.
- 3.24 Hypothetical patients in the best available therapy group were assumed to begin in the best available therapy health state. In this health state, patients had a selection of treatments considered to be best available therapy, which reflects the treatment had by patients in the control group of the COMFORT-II trial. Best available therapy was assumed to give patients some control of symptoms but no control of splenomegaly and little improvement in health-related quality of life. Patients could continue to have best available therapy until death or they could stop (after exhausting possible options) and progress to the supportive care health state. In this health state, patients experienced a gradual worsening

of the disease (symptoms and haematological parameters) and health-related quality of life until death. No formal stopping rule was applied to patients having best available therapy and discontinuation was modelled based on discontinuation seen during the COMFORT-II trial.

- 3.25 Hypothetical patients who entered the model on ruxolitinib were categorised into 4 groups based on their outcomes at 24 weeks in the COMFORT trials. There were 4 categories of response in the model: response, no response, early discontinuation of therapy or early death. Patients whose disease did not respond to treatment were subject to a stopping rule. The company's choice of 24-week stopping rule and decision was based on the [British Committee for Standards in Haematology guideline](#) for the diagnosis and management of myelofibrosis (2012), and also took into account the Summary of Product Characteristics of ruxolitinib which states that treatment should be stopped after 6 months (26 weeks) if there has been no reduction in splenomegaly or improvement in symptoms since starting therapy. The definition of response was based on the International Working Group-Myeloproliferative Neoplasms Research and Treatment/European LeukemiaNet's criteria for treatment response in myelofibrosis guidelines, and defined in terms of either a spleen response or a symptom response. This stopping rule was not applied in the COMFORT-I or COMFORT-II trials.
- 3.26 Clinical-effectiveness data used in the model were mainly taken from the COMFORT-II trial, which enrolled patients with intermediate-2 or high-risk myelofibrosis. Additional data were used from the COMFORT-I trial, which enrolled intermediate-2 and high-risk patients whose disease did not respond to other therapies.
- 3.27 Ruxolitinib dosing was subject to dose-intensity adjustment and varied according to platelet count, patient's tolerance of therapy and efficacy. To reflect this, individual patient data from the COMFORT-II trial were used to estimate dose given. Based on this data, the dose of ruxolitinib used in the model varied between 5 mg and 25 mg twice daily, or 5 mg and 35 mg once per day. For a small proportion of treatment days (1.38%), dose interruptions were also accounted for, that is, 0 mg dose. The most common doses used in the model were 5 mg twice daily (14.50% of treatment days), 10 mg twice a day (25.93% of treatment days), 15 mg twice daily (20.14% of treatment days) and 20 mg twice daily (30.66% of treatment days).

- 3.28 The comparator in the model, best available therapy, consisted of several different treatments for myelofibrosis based on data from the COMFORT-II trial. Dose intensity, duration of treatment or order of treatment were not recorded in the COMFORT-II trial. To account for this lack of data, several assumptions were made when calculating the cost of best available therapy.
- 3.29 In the model, the proportions of patients gaining a spleen response, stopping ruxolitinib treatment, and dying early were based on data from the COMFORT-I and COMFORT-II trials. The proportion of patients gaining symptom response was based on the COMFORT-I trial. Because there were no data to model overall survival and discontinuation rates in a response group that included both patients whose spleen decreased in length by 50% or more and whose symptoms improved, the company assumed that overall survival and discontinuation rates were the same for both arms.
- 3.30 For patients starting best available therapy, death could occur either while on treatment or after stopping best available therapy, when patients had moved to the supportive care state. The number of patients dying on best available therapy was based on data from the COMFORT-II trial and time to death for this group was based on time to stopping therapy.
- 3.31 For all patients starting on ruxolitinib, mortality rates were the same during the initial treatment phase (24 weeks). After 24 weeks, mortality rates differed according to whether their disease responded to treatment, did not respond to treatment, or they stopped treatment during the initial treatment phase. As with best available therapy, patients whose disease responded to ruxolitinib treatment could die either while on treatment or after they had stopped treatment. Data for both ruxolitinib and best available therapy were obtained from the COMFORT-II trial. In the baseline model, the mortality rate for patients whose disease responded to ruxolitinib was assumed to be 0.0%, that is, no patients die while on ruxolitinib. For patients stopping ruxolitinib (both during the initial 24-week period and for patients whose disease responded after this initial period), duration alive after discontinuation was modelled based on survival seen in the COMFORT-II trial.
- 3.32 Patients whose disease did not respond to ruxolitinib were assumed to move to best available therapy after 24 weeks. Mortality was modelled in the same way as patients starting on best available therapy except that patients whose disease

did not respond to ruxolitinib were assumed to have a mortality benefit of an additional 24 weeks of life.

- 3.33 For patients starting on ruxolitinib, the model used 2 alternative discontinuation rates: one for the initial 24-week treatment phase of the model (see section 3.25); and one that was applied after 24 weeks to patients who had a 50% or more reduction in spleen length and improvement in symptoms from baseline, and who continued treatment. Both rates were taken from the COMFORT-II trial. After 24 weeks, the rate of discontinuation was based on analysis of time to discontinuation for patients who had a reduction in spleen length of 50% or more. A range of parametric survival models were considered to extrapolate beyond the observed data, and based on the Akaike information criterion and Bayesian information criterion, a Gompertz distribution was considered the most appropriate. Scenario analyses using the alternative distributions were also presented. A single rate of discontinuation was used for patients on best available therapy, based on data from the COMFORT-II trial, because no stopping rule was applied. As with discontinuation from ruxolitinib, several parametric survival models were tested and the Gompertz distribution was considered to be the most appropriate. The company also presented scenario analyses using alternative distributions.
- 3.34 The model included the possibility of leukaemic transformation. It did this by allowing this to occur as an adverse event with disutility and cost applied. The company used the same rate of leukaemic transformation from the COMFORT-II trial for patients in both the ruxolitinib and best available therapy groups.
- 3.35 The COMFORT-I and COMFORT-II trials did not include a generic measure of health-related quality of life (such as the EQ-5D). However, the company explained that although it would have been possible to do so, it was not considered appropriate to use a mapping algorithm to develop health-related quality of life based on EQ-5D. Instead, a condition-specific preference-based measure for myelofibrosis, the MF-8D, was developed using existing measures, the MF-SAF and EORTC QLQ-C30. The model used changes in health-related quality of life on a continuous scale according to different phases of the myelofibrosis disease state. Patients were assumed to experience constant benefits with ruxolitinib and best available therapy, but health-related quality of life was assumed to steadily decline in the supportive care health state.

- 3.36 The costs associated with managing myelofibrosis were obtained from the Haematological Malignancies Research Network (HMRN) audit and the ROBUST study. The HMRN audit provided information on the number of hospital nights, outpatient visits and laboratory tests. The ROBUST study provided data on resource use. Data from the JUMP study were used to represent the reduction in resource use associated with the use of ruxolitinib. These data were supplemented by information from the COMFORT trials and assumptions when appropriate.
- 3.37 The company presented base-case cost-effectiveness results with and without a patient access scheme (PAS). The deterministic incremental cost-effectiveness ratio (ICER) for ruxolitinib compared with best available therapy with the original PAS was £44,905 per quality-adjusted life year (QALY) gained (incremental costs £112,843, incremental QALYs 2.51).
- 3.38 The company carried out a series of deterministic one-way sensitivity analyses. Most inputs had minimal impact on the ICER estimate, with the exception of post-ruxolitinib discontinuation survival, and the overall survival estimate for best available therapy. However, the estimated ICER did not exceed £50,000 per QALY gained in any of the sensitivity analyses.
- 3.39 The company conducted a series of scenario analyses:
- varying the model time horizon; assuming the best available therapy discontinuation rate followed an exponential, Weibull or log-normal distribution
 - varying the duration on best available therapy, using the ITT overall survival estimate from the COMFORT-II trial
 - changing the post-best-available-therapy discontinuation survival (survival after best available therapy discontinuation) to follow a shape of 1 (compared with 0.63 in the base case)
 - impact of different response criteria
 - discontinuation rate for patients on ruxolitinib achieving a spleen response was assumed to follow alternative distributions and assuming all patients remain on treatment for a maximum duration of 3.5 years, 5 years, 7.5 years and 10 years.

None of these scenarios were found to significantly impact the ICER.

3.40 After consultation on the appraisal consultation document (ACD), the company requested permission which was granted by NICE, to present new evidence and a revised version of the model, which was updated in line with the ERG's critique on the original model. The changes to the assumptions of the original model were:

- Increased PAS discount.
- Correction of the errors, identified by the ERG, on the formula used for including leukaemic transformation.
- Excluded lenalidomide from the basket of treatments that made up best available therapy and replaced with thalidomide.
- Upgraded baseline utility by 10%.
- People whose disease responds to ruxolitinib spend 30% of their time on best available therapy, after stopping ruxolitinib.

This resulted in a revised company base-case ICER of £31,229 per QALY gained (incremental costs £89,428; incremental QALYs 2.86).

3.41 The company also did exploratory analyses that incorporated the impact of ruxolitinib treatment on the quality of life of carers. A 0.1 utility decrement was applied for carers of patients on best available therapy to the utility of the general population. Using the revised company model, this analysis resulted in an ICER of £28,060 per QALY gained (incremental costs £87,633; incremental QALYs 2.84).

3.42 In response to a request from NICE, the company carried out further exploratory analyses to calculate the cost-effectiveness results separately for the 2 subgroups reflected in the model (that is, for the intermediate-2 and high-risk subgroups). This model incorporated separate patient-level data from the COMFORT trials for the intermediate-2 and high-risk subgroups for the following inputs:

- Overall survival on the best available therapy arm, adjusted for crossover using RPSFT method.
- Number of outpatient visits on best available therapy.

- Probability of discontinuation for people whose disease responds (spleen response only) on ruxolitinib.
- Survival after stopping ruxolitinib.
- Treatment dose.
- Change in health-related quality of life.

The results showed that the ICER for the intermediate-2 risk subgroup was £25,896 per QALY gained (incremental costs £124,429; incremental QALYs 4.80) and the ICER for the high-risk subgroup was £37,985 per QALY gained (incremental costs £59,119; incremental QALYs 1.56).

Evidence review group comments

- 3.43 The ERG was satisfied that all relevant studies had been included in the company's submission. The ERG stated that the COMFORT trials were of good quality and appropriate for addressing the decision problem.
- 3.44 The ERG commented that the COMFORT trials only included patients with splenomegaly and intermediate-2 or high-risk myelofibrosis, who had a platelet count of 100×10^9 /litre or more and an absolute neutrophil count of 1×10^9 /litre or more. Also, patients suitable for allogeneic haematopoietic stem cell transplantation (allo-HSCT) at the time of study enrolment were excluded from the trials. Therefore, the population represented in the trials was narrower than that covered by the marketing authorisation.
- 3.45 The ERG stated that overall survival was a secondary end point in both the COMFORT trials and that neither trial had sufficient power to detect a statistically significant difference in overall survival between treatments. The ERG noted that all methods to adjust for crossover have limitations, but the methods used by the company were appropriate.
- 3.46 The ERG considered the economic model in the company submission and the updated model received during consultation (see section 3.40), which included an updated PAS and revised assumptions. It agreed that the increased PAS discount had been correctly applied. The ERG commented that using an individual patient discrete event simulation model can be considered novel because most oncology models are cohort Markov structures. The ERG stated

that using this type of modelling approach appears justified given the progressive nature of the disease and has the advantage of increased flexibility and is appropriate for the decision problem.

- 3.47 The ERG noted that the population in the model pragmatically reflected the patients in COMFORT-II, which represents a subset of the population specified in the marketing authorisation for ruxolitinib, that is, patients with intermediate-2 or high-risk myelofibrosis. The ERG commented that the modelling presented therefore reflects the cost effectiveness of ruxolitinib in this more restricted population.
- 3.48 The ERG had concerns about the composition of best available therapy used in the original model. The clinical adviser to the ERG indicated that lenalidomide is rarely used in the UK, and the HMRN audit appeared to confirm this. The ERG also noted that in the revised model, the company replaced lenalidomide with thalidomide in the basket of therapies that made up best available therapy and agreed that this assumption was plausible. The ERG stated that it was also clear from the published literature that other treatments are used in the UK, which were not included as part of best available therapy. In particular, the [British Committee for Standards in Haematology guideline](#) for the diagnosis and management of myelofibrosis (2012) indicates that allo-HSCT is a potential therapy for myelofibrosis and is the only curative treatment for patients. The ERG was of the opinion that allo-HSCT should have been considered either as part of best available therapy or as an alternative comparator because significant survival benefits have been seen using allo-HSCT. However, the ERG recognised that this treatment option would not be suitable for all patients and has a different treatment goal (curative as opposed to managing symptoms).
- 3.49 The ERG considered the assumption of no drug wastage for ruxolitinib did not accurately reflect drug usage in clinical practice. The ERG had concerns about drug wastage, given that most adverse events are managed by dose reduction or interruption, leading to additional costs.
- 3.50 The ERG considered the company's assumption of 0% mortality with ruxolitinib treatment to be unrealistic. During clarification, the company acknowledged that this assumption may be optimistic. It therefore provided additional scenario analyses assuming either the same probability of death on discontinuation used for the best available therapy group, or assuming a

probability equal to 10%.

3.51 The ERG considered the assumption of upgrading the baseline utility value by 10%. It noted that upgrading the utility value was in line with its critique on the original model, and that this scenario may represent a more realistic estimate of the ICER. However, the ERG raised concerns that a 10% upgrade in utility, based on clinical opinion was associated with substantial uncertainty and considered the following to be equally plausible:

- the unadjusted baseline values
- the 5% upgrading factor, presented in a scenario analysis by the company
- and the 10% upgrading factor.

3.52 The ERG commented on the revised structure of the model and the assumption that patients whose disease responded on the ruxolitinib arm of the model would spend 30% of their time alive on best available therapy, instead of moving directly to supportive care. The ERG acknowledged that in clinical practice, it is likely that a proportion of patients would spend time on best available therapy after stopping ruxolitinib treatment, but it noted that there is minimal evidence available to support it. Regarding the 30% value, the ERG commented that this value seems to be arbitrary. It also commented that the assumption that all patients would move to best available therapy after stopping treatment with ruxolitinib is unlikely to reflect clinical practice. It also considered the assumption that best available therapy would be as effective for patients who stopped ruxolitinib as for patients starting best available therapy to be highly optimistic. The ERG therefore considered the revised structure of the model to be subject to high uncertainty.

3.53 The ERG stated that the results presented by the company for the extensive sensitivity and scenario analyses, based on the original and the revised models, showed the estimated ICER to be largely robust to a range of input values and assumptions made in the model.

Evidence Review Group exploratory analyses

3.54 The ERG noted that the new evidence and the revised model (with the updated PAS) received during consultation addressed several issues raised by the ERG,

including the composition of best available therapy and upgrading baseline utility values. It did further exploratory analyses on the revised model focusing on the discontinuation rate for best available therapy and assumptions around the revised model structure.

3.55 The ERG carried out exploratory analyses on the revised model, in which it incorporated all of its preferred assumptions into the company's revised cost-effectiveness model. The assumptions of the 2 scenarios were:

- Scenario 1 (ERG preferred base case):
 - Time on ruxolitinib is part of the time on best available therapy for people whose disease does not respond to ruxolitinib.
 - No adjustment to baseline utility.
 - Discontinuation rate for best available therapy is reduced by 20%.
 - People move to supportive care after stopping ruxolitinib, in line with the company's original model structure.
- Scenario 2 (all the above assumptions plus the company's preferred base case):
 - Upgrade baseline utility values by 10%.
 - People whose disease responds to ruxolitinib spend 30% of their time alive after stopping ruxolitinib on best available therapy, in line with the company's revised model structure.

The results of the exploratory analyses using these scenarios were an ICER of £35,632 per QALY gained for Scenario 1 and an ICER of £31,676 per QALY gained for Scenario 2.

3.56 The ERG then critiqued on the company's exploratory analyses. It did not consider the carer scenario to be robust because the company used data from studies that were done with a non-UK patient population. It also commented that the utility decrement applied for the carer was based on a study from a different disease area (glioma and other types of cancer) and that the results of this study did not represent a statistically significant change in quality of life. Finally, the ERG considered that the assumption that the quality of life of carers returns to that of the general population during treatment with ruxolitinib to be

overly optimistic. Using its revised assumptions in Scenario 1 (see section 3.53), it calculated the cost-effectiveness result of the exploratory analysis on carers' quality of life. This resulted in an ICER of £31,855 per QALY gained.

- 3.57 The ERG also commented on the exploratory analyses that calculated the ICERs separately for the 2 subgroups: intermediate-2 and high-risk disease. It considered that the implementation of the assumptions was appropriate and that there were significant differences in the ICERs between the subgroups. These were because of the substantial differences between the subgroups in the response and prognosis of patients having ruxolitinib and the minimal differences in prognosis for patients having best available therapy. The ERG also noted that there was no difference between the 2 subgroups in overall survival for patients on the best available therapy arm.

4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of ruxolitinib having considered evidence on the nature of myelofibrosis and the value placed on the benefits of ruxolitinib by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.1 The committee considered the impact of splenomegaly and myelofibrosis on a person's wellbeing and on their families. It heard from the patient and clinical experts how debilitating myelofibrosis can be and that symptoms vary from person to person. The patient experts explained that the 2 most problematic symptoms were extreme fatigue and extreme itch. They described being fatigued to the point of avoiding exercise of any sort, and being unable to socialise and work, which results in emotional and financial pressures for both the person with myelofibrosis and their families. The patient experts commented that extreme itch was a prevalent symptom leading to despair and depression. The committee concluded that improving the symptoms associated with myelofibrosis, particularly fatigue and itching, would greatly benefit the wellbeing of people with myelofibrosis and their families.

4.2 The committee considered the treatment pathway for myelofibrosis and the position of ruxolitinib within it. It heard from the clinical experts that the management of myelofibrosis and disease-related splenomegaly or symptoms varies and that patients regularly change treatment. The committee heard from the clinical experts that allogeneic haematopoietic stem cell transplant (allo-HSCT) is the only potentially curative treatment for myelofibrosis, but is only suitable for people who are fit enough to have treatment. It heard from the experts that allo-HSCT is rarely used as a treatment option because of its mortality risk. The committee heard from the clinical experts that the treatments offered to people who are not fit enough to have allo-HSCT are in line with the [British Committee for Standards in Haematology guidelines](#) for investigation and management of myelofibrosis (2012). The committee was aware that the guideline recommends ruxolitinib as first-line therapy for symptomatic splenomegaly or myelofibrosis-related symptoms. Ruxolitinib is currently available through the Cancer Drugs Fund. The committee was also aware that the guideline recommends that treatment with ruxolitinib should be continued for 24 weeks before deciding whether to stop, and that the decision to stop ruxolitinib therapy should be dependent on a combination of different

factors, including the beneficial effect of treatment on splenomegaly and symptoms. The committee noted that the guideline's recommendation on the 24-week stopping rule was consistent with the treatment discontinuation rule specified in the summary of product characteristics for ruxolitinib. It also noted that the [British Committee for Standards in Haematology guideline](#) recommends hydroxycarbamide, thalidomide plus prednisolone or lenalidomide as alternative medical treatments for people with symptomatic splenomegaly. The committee was aware from the clinical experts that any benefit from hydroxycarbamide is usually short term and that clinicians considered ruxolitinib to be more clinically effective than hydroxycarbamide (among other best available therapies) for symptom control in people with myelofibrosis needing treatment. The committee heard from the clinical experts that thalidomide is used, but that lenalidomide is rarely used. It recognised that ruxolitinib was a valued treatment option.

Clinical effectiveness

- 4.3 The committee considered the evidence presented by the company on the clinical effectiveness of ruxolitinib. It noted that the company had presented 2 randomised controlled trials (RCTs), COMFORT-I and COMFORT-II, which evaluated the efficacy of ruxolitinib in patients who had intermediate-2 or high-risk myelofibrosis (its main source of evidence), and supportive evidence from 4 non-RCT studies of ruxolitinib in patients with intermediate-1 risk myelofibrosis or a low platelet count (ROBUST, JUMP, study 258 and EXPAND). The committee was aware that the COMFORT trials had also been the main source of evidence for NICE's previous technology appraisal guidance on ruxolitinib for disease-related splenomegaly or symptoms in adults with myelofibrosis, but that longer-term data from these trials (COMFORT-I median follow-up 3 years, COMFORT-II median follow-up 3.5 years) had become available since the guidance was published.
- 4.4 The committee discussed the relationship between the marketing authorisation for ruxolitinib and the populations in the COMFORT trials and the 4 non-RCT studies. It noted that the COMFORT trials included only patients who had intermediate-2 or high-risk myelofibrosis with platelet counts over 100×10^9 /litre, but that the marketing authorisation was not defined by risk categories or platelet count. The COMFORT trials only covered a subset of the population covered by the marketing authorisation. The committee noted that

the 4 non-RCT studies included patients with intermediate-1 and intermediate-2 risk myelofibrosis or with platelet counts of $50\text{--}100\times 10^9/\text{litre}$, and noted that these studies provided some evidence for the use of ruxolitinib in a subgroup of patients who were not included in the COMFORT trials but are included in the marketing authorisation for ruxolitinib. The committee concluded that data from the COMFORT trials and the 4 non-RCT studies should be considered, because the data were obtained from populations that are covered by the marketing authorisation for ruxolitinib and so are relevant for decision-making. However, it noted that the company had restricted its economic assessment to the population in the COMFORT-II trial (see section 4.9) and so the committee would use the other studies principally as corroborative evidence.

- 4.5 The committee considered the generalisability of the results from the COMFORT trials and the 4 non-RCT studies. It heard from the clinical experts that ruxolitinib would mostly be used in higher-risk people who had splenomegaly or symptoms. The committee was also aware that the COMFORT trials did not include patients with low platelet counts (under $100\times 10^9/\text{litre}$) but that 2 of the non-RCT studies (study 258 and EXPAND) included patients with platelet counts of between 50 and $100\times 10^9/\text{litre}$. It heard from the clinical expert that clinicians would treat people with a platelet count of more than $100\times 10^9/\text{litre}$ with ruxolitinib (which is reflective of the population in the COMFORT trials) and also people with a platelet count of $50\text{--}100\times 10^9/\text{litre}$ (which is reflective of the population in study 258 and EXPAND), because this is consistent with the summary of product characteristics for ruxolitinib. The clinical experts stated that clinicians may occasionally treat people with platelet counts below $50\times 10^9/\text{litre}$ after careful consideration and informed discussion with the person about the benefits and risks of ruxolitinib, because the summary of product characteristics for ruxolitinib does not provide dosing recommendations for this population. The committee concluded that the results from the COMFORT trials and the non-RCT studies were generalisable to the people who would have treatment with ruxolitinib in England; that is, people with intermediate-2 or high-risk myelofibrosis.
- 4.6 The committee noted that COMFORT-II was the only study included in the company's submission with an active treatment group and discussed whether the comparator group (best available therapy) was relevant to clinical practice in England. The committee noted the evidence review group's (ERG) concerns that

the selection of treatments that made up best available therapy in the trial included lenalidomide (but was replaced with thalidomide in the revised model, based on the [British Committee for Standards in Haematology guideline](#) for investigation and management of myelofibrosis [2012]). The committee heard from the clinical experts that lenalidomide is rarely used in clinical practice in England. It heard that hydroxycarbamide was the main treatment currently used in clinical practice, but people with myelofibrosis are a heterogeneous group and therefore treatments would often be adapted to individual patient needs. The committee concluded that the treatments used in the best available therapy group (including thalidomide but without lenalidomide) in COMFORT-II were clinically relevant.

- 4.7 The committee considered the clinical-effectiveness evidence for ruxolitinib on spleen size and spleen volume. It noted that the COMFORT trials showed that ruxolitinib provided significant benefits for reduction in spleen size and spleen volume. The committee also noted that the results from the 2 non-RCT studies (ROBUST and JUMP) were generally consistent with the results from the COMFORT trials and that the results were similar between patients with intermediate-1 and high-risk myelofibrosis (although the number of patients in the different risk subgroups was low). The committee was aware that there was no direct association between spleen size and symptoms and that a person could have a modest size spleen with severe symptoms or a large spleen with minimal symptoms. It noted that COMFORT-I also assessed symptom reduction, and that the results showed a clinically meaningful improvement in myelofibrosis-associated symptoms for patients who had treatment with ruxolitinib compared with a worsening of symptoms for patients who had placebo. The committee was aware that the results from 2 of the non-RCTs (ROBUST and JUMP) also showed symptom reduction with ruxolitinib and that the results were similar between patients with intermediate-1 risk and high-risk disease (although the number of patients in the different risk subgroups was low). The committee was aware of the emphasis that the patient experts placed on symptoms in myelofibrosis (see section 4.1) and concluded that symptoms (especially itch and fatigue) and spleen size were both important outcomes to consider and that ruxolitinib was effective in reducing spleen size and relieving symptoms in people with intermediate-1, intermediate-2 and high-risk myelofibrosis. It therefore concluded that ruxolitinib was a clinically effective treatment for disease-related splenomegaly or symptoms in adults with myelofibrosis.

- 4.8 The committee considered the overall-survival data. It was aware that the long-term data (median follow-up 3.5 years) from COMFORT-II showed a statistically significant difference in overall survival for ruxolitinib compared with best available therapy, using both the intention-to-treat analysis and the analysis adjusting for crossover. It noted the hazard ratios, which after adjusting for crossover, strongly indicated a survival benefit for ruxolitinib (see [section 3.2](#)). The committee therefore concluded that there was sufficient evidence to show that ruxolitinib increased overall survival compared with best available therapy.
- 4.9 The committee considered the adverse events associated with ruxolitinib. It noted that the company had presented long-term data on adverse events from the COMFORT trials and supporting data from the 4 non-RCT studies. The committee accepted that ruxolitinib was generally well-tolerated and that haematological adverse events were common with ruxolitinib. It heard from the patient experts that the adverse events reported with ruxolitinib were considered manageable by patients. The committee heard from the clinical experts that haematological outcomes (for example, anaemia and thrombocytopenia) are important in managing myelofibrosis. It was aware that ruxolitinib dose reductions rather than transfusions were the main means of treating haematological problems and heard from the clinical experts that the rate of blood transfusions would be equivalent for ruxolitinib and other available treatments for myelofibrosis in clinical practice. The committee concluded that ruxolitinib did have a negative impact on haematological outcomes in the short term for people with myelofibrosis, but agreed that these were manageable.

Cost effectiveness

- 4.10 The committee discussed the company's general approach to developing its economic model. It noted that the ERG considered the company's approach to be well presented and appropriate. It also noted the ERG's comments that the data used in the model was obtained mainly from COMFORT-II and therefore the cost-effectiveness estimates obtained from the model were specific to a population with intermediate-2 or high-risk myelofibrosis. The committee acknowledged that the population in the company's economic model was only a subset of the population covered by the marketing authorisation for ruxolitinib (see [section 4.3](#)), but agreed that the company's model was acceptable for assessing the cost effectiveness of ruxolitinib only for people with

intermediate-2 or high-risk myelofibrosis. It also acknowledged that people with intermediate-1 risk myelofibrosis were not included in the model and therefore it was not able to consider this subgroup in its decision making. The committee also considered the revised model submitted by the company after consultation on the appraisal consultation document and noted that the revised assumptions (see [section 3.52](#)) were in line with the ERG's critique of the original model.

- 4.11 The committee discussed whether the company's assumption of no drug wastage for ruxolitinib was appropriate. It noted that the ERG had provided exploratory analyses on the original model, which allowed for 5%, 10% and 15% wastage of ruxolitinib. The committee heard from the clinical experts that the company's assumption of no drug wastage for ruxolitinib reflected drug usage in clinical practice. It agreed that the ERG's exploratory analyses allowing significant drug wastage for ruxolitinib were not representative of clinical practice. The committee discussed whether the drug costs for patients having treatment with ruxolitinib used in the economic model reflected the drug costs for ruxolitinib in clinical practice. It was aware that the drug costs for ruxolitinib were estimated from the starting doses as defined in the summary of product characteristics for ruxolitinib and the actual dose usage in COMFORT-II. The committee heard from the clinical experts that it was difficult to estimate the drug costs for the 'average' patient seen in clinical practice because the dosage used varied between people and depended on several factors such as platelet count, response to treatment and adverse events. The committee agreed that there was some uncertainty over whether the drug costs for ruxolitinib used in the economic model reflected the drug costs for ruxolitinib in clinical practice, but agreed that the drug costs used were appropriate because they were based on the same trial data on which the effectiveness inputs were based.
- 4.12 The committee discussed the company's revised economic model that included an updated patient access scheme for ruxolitinib, and the ERG's critique of the submission. The committee noted the company's revised base-case incremental cost-effectiveness ratio (ICER) result for ruxolitinib compared with best available therapy of £31,200 per quality-adjusted life year (QALY) gained. It also considered the scenario analyses presented by the ERG, based on the revised cost-effectiveness model from the company. It considered that the assumptions of Scenario 1 and Scenario 2 (see [section 3.55](#)) are clinically plausible, but noted the ERG's concerns about the uncertain evidence on the upgrade of baseline utility value. The committee agreed that the estimated ICER for ruxolitinib was

largely robust to a range of values and model assumptions (based on sensitivity analyses conducted on the original model). The committee did not, however, favour factoring in a modification of the ICERs to reflect carers' quality of life. Although it agreed that carers' health could be affected by caring, it did not consider the results robust; nor did it consider that myelofibrosis stood out amongst severe illnesses in having a more profound carer burden. Most importantly, the committee concluded that the scenario proposed by the company did not take into account the opportunity cost of carers' burden (that is, the carers' burden relieved by other treatments currently available in the NHS that ruxolitinib might displace).

- 4.13 The committee considered the most plausible ICER for people with intermediate-2 or high risk myelofibrosis. It also considered it important to evaluate the cost effectiveness of ruxolitinib separately for the different subgroups (intermediate-2 and high-risk myelofibrosis) because of the different prognosis and response to therapy in these groups. It was aware of the uncertainty in the values in section 3.42 and noted the ERG's critique of the additional analyses in section 3.57. It considered that the subgroup analysis provided by the company was appropriate. The committee noted that the ICER for the intermediate-2 subgroup was £26,000 per QALY gained, which is within the range normally considered as cost effective. The committee therefore considered ruxolitinib to be a cost-effective option for treating disease-related splenomegaly or symptoms in intermediate-2 risk myelofibrosis. It also noted that the ICER for the high-risk subgroup was £38,000 per QALY gained.
- 4.14 Because the ICER for people with high-risk myelofibrosis was above £30,000 per QALY gained, the committee discussed whether ruxolitinib fulfilled the criteria for a life-extending, end-of-life treatment. The committee considered the supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all the following criteria must be met:
- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
 - There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.

- The treatment is licensed or otherwise indicated for small patient populations.

In addition, when taking these criteria into account, the committee must be persuaded that the estimates of the extension to life are robust and that the assumptions used in the reference case of the economic modelling are plausible, objective and robust.

- 4.15 The committee discussed the criterion of a small patient population. It accepted the estimates in the company's submission that 1,185 people are estimated to be living with myelofibrosis in England and would be eligible for treatment with ruxolitinib for disease-related splenomegaly or symptoms associated with myelofibrosis. The committee concluded that the eligible population for England did not exceed 7,000 and that ruxolitinib met the end-of-life criterion for a small patient population.
- 4.16 The committee discussed the criterion of extension to life of more than an average of 3 months. It noted that because median overall survival was not reached in the ruxolitinib group it was not possible to calculate the median (or mean) survival benefit associated with ruxolitinib compared with best available therapy in the COMFORT-II trial. However, it noted the results of an indirect comparison analysis between the ruxolitinib treatment group of COMFORT-II and the Dynamic International Prognostic Scoring System (DIPSS) cohort. It noted that this analysis produced estimates of median survival of 5 years from diagnosis on ruxolitinib compared with 3.5 years for the DIPSS cohort. The committee concluded that treatment with ruxolitinib provided an extension of life of more than an average of 3 months.
- 4.17 The committee discussed whether people with disease-related splenomegaly or symptoms associated with myelofibrosis would be expected to have a mean life expectancy of less than 24 months. It was aware that median overall survival in the best available therapy group of COMFORT-II was 28 months in people with intermediate-2 or high-risk disease. The committee gave further consideration to the range and relevance of the evidence available on the expected survival of people with high-risk disease from the various prognostic scoring systems (International Prognostic Scoring System [IPSS] for primary myelofibrosis, DIPSS and DIPSS-plus). It noted that the company's submission reported that median survival using the various prognostic scoring systems varied from a median of 1.3 to 2.3 years for people with high-risk myelofibrosis. The committee acknowledged that there was some uncertainty about the life expectancy of people with myelofibrosis but agreed that the various prognostic

scoring systems provided the best available evidence because the data were based on patients before they had any treatment. The committee considered whether the life expectancy of patients with high-risk myelofibrosis met the end-of-life criterion of less than 24 months and was persuaded that the life expectancy for people with high-risk myelofibrosis was likely to be less than 24 months. The committee therefore concluded that it had been provided with evidence that high-risk patients met all of the end-of-life criteria and considered ruxolitinib to be a cost-effective option for treating disease-related splenomegaly or symptoms in high-risk myelofibrosis.

4.18 The committee considered whether ruxolitinib is an innovative treatment. It agreed that ruxolitinib provided a step change in treating splenomegaly and symptoms in people with myelofibrosis. The committee acknowledged that ruxolitinib is a targeted treatment and manages symptoms for which there is currently no available treatment. Therefore, the committee agreed that ruxolitinib is innovative, but there were no additional gains in health-related quality of life over those already included in the QALY calculations.

4.19 The committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism, and accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The committee heard nothing to suggest that there is any basis for taking a different view with regard to the relevance of the PPRS to this appraisal. It concluded that the PPRS payment mechanism was not relevant for its consideration of the cost effectiveness of any of the technologies in this appraisal.

Summary of appraisal committee's key conclusions

TA386	Appraisal title: Ruxolitinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis	Section
Key conclusion		

<p>Ruxolitinib is recommended as an option for treating disease-related splenomegaly or symptoms in adults with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis, only:</p> <ul style="list-style-type: none"> • in people with intermediate-2 or high-risk disease, based on International Prognostic Scoring System (IPSS) prognostic factors and • if the company provides ruxolitinib with the discount agreed in the patient access scheme. 		1.1
<p>The committee concluded that the most plausible incremental cost-effectiveness ratios (ICERs) for people with intermediate 2 or high-risk myelofibrosis were £26,000 per quality-adjusted life year (QALY) gained for the intermediate 2 risk subgroup and £38,000 per QALY gained for the high-risk subgroup.</p>		4.12
<p>Because the ICER for patients with high-risk myelofibrosis was above £30,000 per QALY gained, the committee discussed whether ruxolitinib fulfilled the criteria for a life-extending, end-of-life treatment. The committee concluded that it had been provided with evidence that high-risk patients met all of the end-of-life criteria.</p>		4.13–4.16
<p>The committee also acknowledged that people with intermediate -1 risk myelofibrosis were not included in the economic model and therefore it was not able to consider this subgroup in its decision making.</p>		4.9
<p>Current practice</p>		
<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>The committee considered the impact of splenomegaly and myelofibrosis on a person's wellbeing and on their families. It concluded that improving the symptoms associated with myelofibrosis, particularly fatigue and itching, would greatly benefit the wellbeing of people with myelofibrosis and their families.</p>	4.1
<p>The technology</p>		

Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	This appraisal is a review of NICE's previous technology appraisal guidance on ruxolitinib for disease-related splenomegaly or symptoms in adults with myelofibrosis, which was published in June 2013.	-
	Ruxolitinib is currently available through the Cancer Drugs Fund. The committee was aware from the clinical experts that clinicians considered ruxolitinib to be more clinically effective than hydroxycarbamide (among other best available therapies) for symptom control in people with myelofibrosis needing treatment. The committee heard from the clinical experts that thalidomide is used, but that lenalidomide is rarely used. It recognised that ruxolitinib was a valued treatment option.	4.2
	The committee considered ruxolitinib to be innovative because it is a step change in treating splenomegaly and symptoms in people with myelofibrosis, there were no additional gains in health-related quality of life over those already included in the QALY calculations.	4.17
What is the position of the treatment in the pathway of care for the condition?	The committee was aware that the British Committee for Standards in Haematology guideline recommends ruxolitinib as first-line therapy for symptomatic splenomegaly or myelofibrosis-related symptoms. The committee was also aware that the guideline recommends that treatment with ruxolitinib should be continued for 24 weeks before deciding whether to stop, in accordance with the discontinuation rule specified in the summary of product characteristics for ruxolitinib. It recognised that ruxolitinib was a valued treatment option.	4.2
Adverse reactions	Adverse reactions for ruxolitinib are anaemia, thrombocytopenia, neutropenia, bleeding and weight gain.	2.2

	The committee accepted that ruxolitinib was generally well-tolerated and that haematological adverse events were common with ruxolitinib. The committee concluded that ruxolitinib did have a negative impact on haematological outcomes in the short term for people with myelofibrosis, but agreed that these were manageable.	4.8
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	<p>The committee noted that the company had presented 2 randomised controlled trials, COMFORT-I and COMFORT-II, which evaluated the efficacy of ruxolitinib in patients who had intermediate-2 risk or high-risk myelofibrosis as its main source of evidence and supportive evidence from 4 non-randomised controlled trials (non-RCTs) of ruxolitinib in patients with intermediate-1 risk myelofibrosis or a low platelet count (ROBUST, JUMP, study 258 and EXPAND).</p> <p>The committee was aware that the COMFORT trials had been the main source of evidence for NICE's previous technology appraisal guidance on ruxolitinib for disease-related splenomegaly or symptoms in adults with myelofibrosis, but that longer-term data from these trials had become available since the publication of the guidance.</p>	4.3
Relevance to general clinical practice in the NHS	The committee considered the COMFORT-II to be the most clinically relevant study because ruxolitinib had been compared with an active comparator (best available therapy).	4.5
	The committee also concluded that the results from the COMFORT trials and the non-RCTs were generalisable to the people who would have treatment with ruxolitinib in England; that is, people with intermediate 2 or high-risk myelofibrosis.	4.4
Uncertainties generated by the evidence	None identified.	-

<p>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</p>	<p>The committee considered the evidence presented by the company on the clinical effectiveness of ruxolitinib in intermediate-1, intermediate-2 and high-risk myelofibrosis. It noted that the COMFORT trials were the main source of evidence. It also noted that the COMFORT trials only covered a subset of the population covered by the marketing authorisation and that the company had restricted its economic assessment to the population in the COMFORT-II trial (see section 4.9) and so the committee considered the other studies principally as corroborative evidence.</p>	<p>4.4</p>
<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>The COMFORT trials showed that ruxolitinib provided significant benefits for reduction in spleen size and spleen volume. COMFORT-I also assessed symptom reduction and the results showed a clinically meaningful improvement in myelofibrosis-associated symptoms for patients who had treatment with ruxolitinib compared with a worsening of symptoms for patients who had placebo. The committee therefore concluded that ruxolitinib was a clinically effective treatment for disease-related splenomegaly or symptoms in adults with myelofibrosis.</p>	<p>4.6</p>
	<p>The committee considered the overall-survival data. It was aware that the long-term data (median follow-up 3.5 years) from COMFORT II showed a statistically significant difference in overall survival for ruxolitinib compared with best available therapy, using both the intention-to-treat analysis and the analysis adjusting for crossover. It noted the hazard ratios, which after adjusting for crossover, strongly indicated a survival benefit for ruxolitinib.</p>	<p>4.7</p>

<p>For reviews (except rapid reviews): How has the new clinical evidence that has emerged since the original appraisal (TA289) influenced the current (preliminary) recommendations?</p>	<p>Longer-term overall-survival data (COMFORT-I median follow-up 3 years, COMFORT-II median follow-up 3.5 years) became available since the publication of the previous appraisal of ruxolitinib. The committee considered longer follow up of trial data presented in the original appraisal (TA289). It considered ruxolitinib to be a clinically effective treatment for disease-related splenomegaly or symptoms in adults with myelofibrosis, in: people with intermediate-2 and high-risk disease.</p>	<p>4.3</p>
<p>Evidence for cost effectiveness</p>		
<p>Availability and nature of evidence</p>	<p>The committee discussed the company's general approach to be well presented and appropriate. It also noted the ERG's comments that the data used in the model was obtained mainly from COMFORT-II and therefore the cost-effectiveness estimates obtained from the model were specific to a population with intermediate-2, or high-risk myelofibrosis. The committee acknowledged that the population in the company's economic model was only a subset of the population covered by the marketing authorisation for ruxolitinib, but agreed that the company's model was acceptable for assessing the cost effectiveness of ruxolitinib for people with intermediate-2 or high-risk myelofibrosis.</p>	<p>4.9</p>
<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>The committee agreed that there was some uncertainty over whether the drug costs for ruxolitinib used in the economic model reflected the drug costs for ruxolitinib in clinical practice, but agreed that the drug costs used were appropriate because they were based on the same trial data on which the effectiveness inputs were based.</p>	<p>4.10</p>

<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>No issues identified.</p> <p>The committee concluded that there were no additional gains in health-related quality of life over those already included in the QALY calculations.</p>	<p>-</p> <p>4.17</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>After consultation on the ACD, the company requested permission which was granted by NICE, to present new evidence, a revised version of the model and an updated patient access scheme (PAS). The committee considered the results of this analysis, which estimated the ICER in the combined subgroup (intermediate-2 and high-risk) to be £31,200 per QALY gained.</p> <p>Following a request from NICE the company presented evidence on the cost effectiveness of ruxolitinib in the intermediate-2 and high-risk subgroups. The ICER for patients with intermediate-2 risk myelofibrosis was £26,000 per QALY gained, and for the high-risk subgroup was £38,000 per QALY gained.</p>	<p>4.11, 4.12</p>
<p>What are the key drivers of cost effectiveness?</p>	<p>The committee agreed that the estimated ICER for ruxolitinib was largely robust to a range of values and assumptions made to the model.</p>	<p>4.11</p>
<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>The committee concluded that the most plausible ICER for patients with intermediate-2 risk myelofibrosis was £26,000 per QALY gained, and for the high-risk subgroup was £38,000 per QALY gained.</p>	<p>4.12</p>

<p>For reviews (except rapid reviews): How has the new cost-effectiveness evidence that has emerged since the original appraisal (TA289) influenced the current (preliminary) recommendations?</p>	<p>With the PAS included, ruxolitinib was now considered to be a cost effective use of NHS resources for people with intermediate-2 risk and high-risk myelofibrosis.</p>	<p>4.12, 4.16</p>
<p>Additional factors taken into account</p>		
<p>Patient access schemes (PPRS)</p>	<p>The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of ruxolitinib with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.</p>	<p>2.3</p>
	<p>The committee concluded that the PPRS payment mechanism was not relevant for its consideration of the cost effectiveness of any of the technologies in this appraisal.</p>	<p>4.18</p>
<p>End-of-life considerations</p>	<p>The committee concluded that the eligible population for England did not exceed 7,000 and that ruxolitinib met the end-of-life criterion for a small patient population.</p> <p>The committee concluded that treatment with ruxolitinib provided an extension of life of more than an average of 3 months.</p> <p>The committee then considered whether the life expectancy of patients with high-risk myelofibrosis met the end-of-life criterion of less than 24 months and was persuaded that the life expectancy for people with high-risk myelofibrosis was likely to be less than 24 months.</p>	<p>4.14, 4.15, 4.16</p>

Equalities considerations and social value judgements	The potential equality issues identified during the ACD consultation have been noted by the committee. None of these issues related to protected characteristics, as defined by the Equality Act (2010), and so were not considered equality issues.	-
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5 Implementation

- 5.1 Section 7(6) of the [National Institute for Health and Care Excellence \(Constitution and Functions\)](#) and the [Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 5.2 The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.
- 5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has high-risk myelofibrosis and the doctor responsible for their care thinks that ruxolitinib is the right treatment, it should be available for use, in line with NICE's recommendations.
- 5.4 The Department of Health and Novartis have agreed that ruxolitinib will be available to the NHS with a patient access scheme which makes it available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to the Novartis commercial operations team on 01276 698717 or commercial.team@novartis.com.

6 Review of guidance

- 6.1 The guidance on this technology will be considered for review 3 years after publication of the guidance. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Dillon
Chief Executive
March 2016

7 Appraisal committee members, guideline representatives and NICE project team

Appraisal committee members

The appraisal committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the committee members who took part in the discussions for this appraisal appears below. There are 4 appraisal committees, each with a chair and vice chair. Each appraisal committee meets once a month, except in December when there are no meetings. Each committee considers its own list of technologies, and ongoing topics are not moved between committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor Andrew Stevens

Chair of appraisal committee C, Professor of Public Health, University of Birmingham

Professor Eugene Milne

Vice Chair of appraisal committee C, Director of Public Health, City of Newcastle upon Tyne

Professor Kathryn Abel

Institute of Brain and Behaviour Mental Health, University of Manchester

Mr David Chandler

Lay Member

Ms Gail Coster

Advanced Practice Sonographer, Mid Yorkshire Hospitals NHS Trust

Professor Peter Crome

Honorary Professor, Department of Primary Care and Population Health, University College London

Professor Rachel A Elliott

Lord Trent Professor of Medicines and Health, University of Nottingham

Dr Nigel Langford

Consultant in Clinical Pharmacology and Therapeutics and Acute Physician, Leicester Royal Infirmary

Dr Andrea Manca

Health Economist and Senior Research Fellow, University of York

Dr Patrick McKiernan

Consultant Paediatrician, Birmingham Children's Hospital

Dr Iain Miller

Founder and Chief Executive Officer, Health Strategies Group

Professor Stephen O'Brien

Professor of Haematology, Newcastle University

Dr Anna O'Neill

Deputy Head of Nursing and Healthcare School/Senior Clinical University Teacher, University of Glasgow

Professor Peter Selby

Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

Professor Matt Stevenson

Technical Director, School of Health and Related Research, University of Sheffield

Dr Paul Tappenden

Reader in Health Economic Modelling, School of Health and Related Research, University of Sheffield

Professor Robert Walton

Clinical Professor of Primary Medical Care, Barts and The London School of Medicine & Dentistry

Dr Judith Wardle

Lay Member

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Helen Tucker and Boglarka Mikudina

Technical Leads

Nicola Hay and Eleanor Donegan

Technical Advisers

Lori Farrar and Stephanie Yates

Project Managers

8 Sources of evidence considered by the committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by the Centre for Reviews and Dissemination and the Centre for Health Economics, York:

- Hodgson R, Wade R, Biswas M et al. Ruxolitinib for disease-related splenomegaly or symptoms in adults with myelofibrosis (review of TA289): A Single Technology Appraisal. CRD and CHE Technology Assessment Group, August 2015

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to make written submissions. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Company:

- Novartis Pharmaceuticals

II. Professional/expert and patient/carer groups:

- Leukaemia CARE
- MPN Voice
- Association of Cancer Physicians
- British Society for Haematology
- Cancer Research UK
- Royal College of Pathologists
- Royal College of Physicians
- Royal College of Radiologists

III. Other consultees:

- Department of Health

- NHS England
- NHS Hammersmith and Fulham Clinical Commissioning Group
- NHS South Norfolk Clinical Commissioning Group
- Welsh Government

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Institute of Cancer Research
- National Cancer Research Institute
- NHS Centre for Reviews & Dissemination and Centre for Health Economics – York
- National Institute for Health Research Health Technology Assessment Programme
- National Collaborating Centre for Cancer

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on NICE's technology appraisal guidance on ruxolitinib by attending the initial committee discussion and providing a written statement to the committee. They were also invited to comment on the ACD.

- Professor Claire Harrison, Consultant Haematologist, nominated by the Royal College of Pathologists – clinical expert
- Dr Tim Somerville, Honorary Consultant in Haematology, nominated by Novartis Pharmaceuticals – clinical expert
- Colin Clayton, nominated by MPN Voice – patient expert
- Caroline Thomas, Patient Advocate, nominated by MPN Voice – patient expert

E. Representatives from the following company attended committee meetings. They contributed only when asked by the committee chair to clarify specific issues and comment on factual accuracy.

- Novartis Pharmaceuticals

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Accreditation

