NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

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

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using ruxolitinib in the NHS in England. The Appraisal Committee has considered the evidence submitted and the views of non-company consultees and commentators, and clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this appraisal (see section 9) and the public. This document should be read along with the evidence base (the Committee papers)

The Appraisal Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The Appraisal Committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the Committee will also consider comments made by people who are not consultees.
- After considering these comments, the Committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using ruxolitinib in the NHS in England.

For further details, see the Guide to the technology appraisal process.

The key dates for this appraisal are:

Closing date for comments: 10 November 2015

Second Appraisal Committee meeting: 18 November 2015

Details of membership of the Appraisal Committee are given in section 8, and a list of the sources of evidence used in the preparation of this document is given in section 9.

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

1 Appraisal Committee's preliminary recommendations

1.1 Ruxolitinib is recommended as an option for treating disease-related splenomegaly or symptoms in adults with myelofibrosis, only in:

- people with 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/mm^3 and 200,000/mm^3, and 20 mg twice daily for patients with a platelet count of more than 200,000/mm^3.

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 £3600 for a 60-tablet pack of 15 mg or 20 mg tablets, or £1800 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 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 The company's submission

The Appraisal Committee (section 8) considered evidence submitted by Novartis and a review of this submission by the Evidence Review Group (ERG; section 9).

Clinical effectiveness evidence

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

Overview of the randomised controlled trials

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 treatment group; 30.5% of placebo treatment 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 $100x10^9$/L and a palpable spleen length of at least 5 cm. The duration of the study was 24 weeks, after which patients could enter an open-label extension phase. In COMFORT-I, patients were eligible to crossover to ruxolitinib treatment. Before week 24, patients on placebo 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 hydoxycaramide, prednisolone and epoetin alfa. Other treatment used as best available therapy included lenalidomide and thalidomide. All patients on the trial had

intermediate-2 risk or high-risk myelofibrosis, a platelet count of at least $100x10^9$/L and a palpable spleen length of at least 5 cm. The company stated that the trial population may be heathier than the general population with myelofibrosis because of the exclusion criteria of the trial which included uncontrolled hypertension, unstable angina and a life expectancy of less than 6 months. The duration of the trial was 48 weeks, after which patients could enter an open-label extension phase. In COMFORT-II, patients were eligible to crossover to ruxolitinib treatment. Patients on 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 a splenectomy) 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 measure for the primary efficacy outcome was taken 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 reduction, 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 Patients were analysed on an intention-to-treat (ITT) basis for all efficacy endpoints. Patients who discontinued treatment or crossed

over before 24 weeks (in COMFORT-I), or did not have a 48-week assessment of spleen volume (in COMFORT-II because of discontinuation and entering the open-label extension phase) were counted as patients whose disease did not respond (for change in spleen volume and symptom score).

3.7 In COMFORT-I, a statistically significantly greater portion 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% vs. 0.7%, $p < 0.001$). In COMFORT-II, a statistically significantly greater portion 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% vs.0%, $p < 0.001$). In COMFORT-I, a statistically significantly greater portion 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% vs.5.3%, $p < 0.001$). This outcome was not collected in COMFORT II.

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

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 intervals [CI] 0.25 to 0.98) and 102 weeks (HR 0.58, 95% CI 0.36 to 0.95). At a median follow up of 3 years, 42 patients in the ruxolitinib group and 54 patients in the placebo group had died and the difference in overall survival was no longer statistically significant (HR 0.69, 95% CI 0.46 to 1.03). As crossover was permitted during the treatment period of the study, the company provided an analysis 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 performed at median follow up of 3.5 years, which included additional survival information for 15 of 41 patients who were previously deemed lost to follow up. At 3.5 years of follow up, 27% (40 patients) in the ruxolitinib group and 40% (30 patients) in the 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 has 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 As the majority of patients randomised to best available therapy crossed over to ruxolitinib (at a median of 66 weeks); the company was asked during the clarification stage to provide an overall survival analysis with adjustment for crossover using the RPSFT 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 therefore is 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 would need 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 number of observed deaths in the 2 cohorts were 30 (30%) on ruxolitinib and 256 (86%) on conventional care, generating estimates of median survival of 5 years from diagnosis (95% CI 2.9 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 28 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 a greater number of grade 3 or 4 adverse events with ruxolitinib compared with best available therapy (42% compared with 25%). There were a similar number of grade 3 or 4 thrombocytopenia with ruxolitinib compared with best available therapy (8% compared with 7%). Treatment was discontinued 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 While symptom reduction was not specifically assessed in the COMFORT-II trial, the company undertook a post hoc exploratory analysis of health-related quality of life and symptom analyses on the primary analysis data set (at 48 weeks) from COMFORT-II. Of

the 9 symptom scores assessed by the 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). ROBUST 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 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 were seen as early as week 4 and were maintained during the study. Ruxolitinib was generally well-tolerated, with 14% of patients discontinuing treatment as a result of adverse events. The most common grade 3 or 4 haematological adverse events were anaemia (33.0%), thrombocytopenia (12.5%) and neutropenia (3.9%); each of these rarely led to discontinuation of ruxolitinib. The incidences of grade 3 or 4 non-haematological adverse events were low.

3.19 The JUMP study included patients with low platelet counts (at least 50 to under $100x10^9$/L). In this patient population, ruxolitinib was initiated at a dose of 5 mg twice daily. This could be increased to 10 mg twice daily at week 4 in patients with inadequate efficacy, if platelet counts were at least $50x10^9$/L 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 have been reported. At this time point, 82% of patients (31 of 38 patients starting therapy on 5 mg twice daily) remained on the 5 mg twice daily dose and 18% had had 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). The

reduction in splenomegaly and improvements in symptoms observed in this subgroup of patients are however inferior to those achieved for the overall JUMP population. Overall, the adverse effect profile was consistent with previous studies in patients with platelet counts under $100x10^9$/L. The most common grade 3 or 4 haematological adverse events were thrombocytopenia (30%) and anaemia (28%): 3 patients (6%) discontinued because of thrombocytopenia and 1 patient discontinued 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%) discontinued therapy because of adverse events. The company commented that this analysis suggested that ruxolitinib doses of 5 to 10 mg twice daily were generally well tolerated and efficacious in patients with myelofibrosis who have platelet counts of at least 50 to under $10x10^9$/L.

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 $100x10^9$/L). Patients were started at a dose of 5 mg twice daily, with the option to increase to 10 mg twice daily if platelet counts remained adequate. An interim analysis of data from this study reported that by week 24, 62% of patients achieved stable doses of at least 10 mg twice daily. A median percentage reduction in spleen volume of 24.2% was achieved at 24 weeks and 20% of patients achieved a reduction in spleen volume of at least 35.0%. 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 observed 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 $75x10^9$/L or less. Two patients discontinued 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, initiated at a dose of 5 mg twice daily, can benefit patients with low platelet counts.

3.22 EXPAND was an open-label, phase Ib, dose-finding study, which investigated the optimum dose of ruxolitinib in patients with low baseline platelet counts. This ongoing study investigates 15 mg twice daily in patients with platelet counts of 75 to $99x10^9$/L and doses of up to 10 mg twice daily in patients with the lower platelet levels. Results for a preliminary analysis of data for 34 patients have shown that most (97%) patients achieved reductions in palpable spleen length and 50% of patients achieved a reduction in spleen length of at least 50% as their best response. Improvements in symptoms, as assessed using the MF-SAF total symptom score, were also observed; a reduction from baseline of at least 50% at any time in total symptom score was achieved by 43% (6/14) of patients with platelet counts of 75 to $99x10^9$/L and 66.7% (8/12) of patients with platelet counts of 50 to $74x10^9$/L. The reported

adverse effects were consistent with the known safety profile of ruxolitinib.

Cost-effectiveness evidence

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, as this was the shortest unit of time in the model. The company based the analysis from an NHS and personal social services perspective, and costs and benefits were discounted at an annual rate of 3.5%. There were 4 heath states in the model: on ruxolitinib; on best available therapy; on supportive care or 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 received by patients in the control group of the COMFORT-II trial. Patients on best available therapy were assumed to achieve some control of symptoms but not splenomegaly. Patients could continue to have best available therapy until death or they could stop having best available therapy (after exhaustion of possible options) and progress to the supportive care health state. In this health state patients experienced a gradual worsening of the disease (symptoms and haematological parameters) and health-related quality of life until death. No formal stopping rule was applied to patients receiving best available therapy and discontinuation was modelled on discontinuation observed 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 and patients whose disease did not respond to treatment were subject to a stopping rule. This stopping rule was based on criteria set out in the International Working Group for Myelofibrosis Research and Treatment/European LeukemiaNet guidelines. This stopping rule was not applied in COMFORT-I or COMFORT-II trials. There were 4 categories of response in the model: responders, non-responders, early discontinuation group or early death group.

3.26 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. Additional data was 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 to 25 mg twice daily, or 5 mg and 35 mg once per day. For a small proportion of treatment days (1.38%) dose interruptions were also accounted for, that is 0 mg dose. The most common doses used in the model were 5 mg twice daily (14.50% of treatment days), 10 mg twice a day (25.93% of treatment days), 15 mg twice daily (20.14% of treatment days) and 20 mg twice daily (30.66% of treatment days).

3.28 The comparator in the model, best available therapy, consisted of a number of different treatments for myelofibrosis based on data from the COMFORT-II trial. Dose intensity, duration, treatment or order

of treatment were not recorded in the COMFORT-II trial. For the purpose of calculating cost of best available therapy a number of assumptions were made to account for this lack of data.

3.29 Patients who received ruxolitinib had a stopping rule at 24 weeks. The 24 week stopping rule and decision was based on the British Committee for Standards in Haematology (BCSH, 2012) guideline that state that treatment should be discontinued after 6 months if there has been no reduction in splenomegaly or improvement in symptoms since initiation of therapy. The definition of response was based on the International Working Group-Myeloproliferative Neoplasms Research and Treatment criteria for treatment response in myelofibrosis guidelines, and defined in terms of either a spleen response or a symptom response.

3.30 Within the model, the proportions of patients gaining a spleen response, discontinuing ruxolitinib treatment, and experiencing early death were based on data from the COMFORT-I and II trials. The proportion of patients gaining symptom response was based on the COMFORT-I trial. As 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.

3.31 For patients starting on best available therapy, death could occur either whilst on treatment, or after discontinuation of 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 discontinuation of therapy. After the initial treatment phase, patients whose disease responded to treatment, those whose didn't, and those who stopped treatment early each faced different mortality rates. As with best available therapy,

patients whose disease responded to ruxolitinib treatment could die either while on treatment or after they had discontinued treatment. Data for both of these 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 discontinuing ruxolitinib (both during the initial 24 week period and for patients whose disease responded after this initial period), duration alive following discontinuation was modelled based on observed survival 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 receive a mortality benefit of an additional 24 weeks of life.

3.33 The company presented a scenario analysis in which time on ruxolitinib was assumed to be part of the time patients would have been treated with best available therapy. Patients whose disease did not respond were therefore treated as far as possible as if they had never received ruxolitinib.

3.34 For patients starting on ruxolitinib, the model used 2 alternative discontinuation rates, one for the initial 24 week treatment phase of the model, and one which was applied to patients who had a reduction of 50% or more in spleen length and whose symptoms improved (who continue treatment) after 24 weeks. Both rates were obtained 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 Akaike information

criteria (AIC) and Bayesian information criterion (BIC), a Gompertz distribution was considered the most appropriate. Scenario analyses using the alternative distributions were also presented. A single rate of discontinuation was used for patients on best available therapy, based on data from the COMFORT-II trial, as no stopping rule was applied. As with discontinuation from ruxolitinib, a number of parametric survival models were considered. The Gompertz distribution was found to be the most appropriate. The company also presented scenario analyses using alternative distributions.

3.35 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.

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

3.37 The costs associated with management of the myelofibrosis were obtained from the Haematological Malignancies Research Network (HMRN) audit and the ROBUST study. The HMRN audit provided

information on the number of hospital nights, outpatient visits and laboratory tests. 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.

3.38 The company presented base case cost effectiveness results with and without the patient access scheme (PAS). The deterministic incremental cost effectiveness ratio (ICER) for ruxolitinib compared with best available therapy with the patient access scheme was £44,905 per quality- adjusted life year (QALY) gained (incremental costs £112,843, incremental QALYs 2.51). With the patient access scheme there was a 0.33%, 4.32%, 95.02% and 100% probability of ruxolitinib being cost effective if the maximum acceptable ICER was £30,000, £40,000, £50,000 and £60,000 per QALY gained respectively.

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

3.40 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 to 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.

Evidence Review Group comments

3.41 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.

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

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

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

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

3.46 The ERG had a number of concerns about the composition of best available therapy used in the model. The clinical adviser to the ERG indicated that lenalidomide is rarely used in the UK, and the HMRN audit appeared to confirm this. The ERG stated that it was also clear from the published literature that there are other treatments used in the UK which are not included as part of best available therapy. In particular, the British Committee for Standards in Haematology (2012) guideline indicates that allogeneic haematopoietic stem cell transplant (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 as significant survival benefits have been observed using allo-HSCT. However, the ERG recognised that this treatment option would not be suitable for all patients and has a different treatment goal (curative as opposed to management of symptoms).

3.47 The ERG considered the assumption of no drug wastage for ruxolitinib to 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.

3.48 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%.

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

ERG exploratory analyses

3.50 The ERG did further exploratory analyses focusing on: assumptions around drug wastage (assuming a 5%, 10% and 15% wastage of ruxolitinib), lenolidomide replaced with hydroxycarbamide as part of best available therapy, and assumptions around the mortality rate of people whose disease responded to treatment with ruxolitinib.

3.51 The ERG's exploratory deterministic base case ICER with the patient access scheme for ruxolitinib compared with best available therapy (incremental costs £112,682, incremental QALYs 2.52) was £44,831per QALY gained. With the patient access scheme there was a 0.0%, 0.3%, 66.2% and 100% probability of ruxolitinib being cost effective if the maximum acceptable ICER was £30,000, £40,000, £50,000 and £60,000 per QALY gained respectively.

3.52 The ERG's exploratory deterministic ICER with the patient access scheme and without lenolidomide as part of best available therapy for ruxolitinib compared with best available therapy (incremental costs £112,999, incremental QALYs 2.52) was £45,077per QALY gained. The ERG's exploratory deterministic ICER with the patient access scheme and assuming 15% wastage of ruxolitinib compared with best available therapy (incremental costs £128,651, incremental QALYs 2.52) was £51,184 per QALY gained.

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

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

3.54 The ERG's preferred analysis gave a probabilistic ICER with the patient access scheme for ruxolitinib compared with best available therapy (incremental costs £118,820, incremental QALYs 2.45) was £48,553 per QALY gained.

3.55 Full details of all the evidence are in the Committee papers.

4 Consideration of the evidence

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 be greatly beneficial to 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. The Committee heard from clinical experts that the management of patients with myelofibrosis and splenomegaly or symptoms varies and that patients change treatment regularly. 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. The Committee 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 BCSH guideline (2012) 'for the diagnosis and management of myelofibrosis'. 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 drug fund, as NICE

Technology appraisal guidance 289 does not recommend ruxolitinib for the treatment of myelofibrosis. The Committee was also aware that the guideline recommends that treatment with ruxolitinib should be continued for 24 weeks before deciding whether to discontinue 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 regarding the 24-week stopping rule was consistent with the treatment discontinuation rule specified in the summary of product characteristics for ruxolitinib. The Committee also noted that the guideline recommends hydroxycarbamide, thalidomide plus prednisolone or lenalidomide as alternative medical treatments for patients 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 superior to hydroxycarbamide (among other best available therapies) for symptom control in patients with myelofibrosis needing treatment. The committee heard from the clinical experts that thalidomide is used, but that lenalidomide is rarely used. The Committee 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. The Committee 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 risk or high-risk myelofibrosis as its main source of evidence and supportive evidence from 4 non-RCT studies of ruxolitinib in patients with intermediate-risk myelofibrosis or a low platelet count

(ROBUST, JUMP, study 258 and EXPAND). The Committee was aware that the COMFORT trials had been the main source of evidence for NICE's previous appraisal of ruxolitinib (TA289) 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 publication of the previous appraisal of ruxolitinib. The Committee was also aware that the 4 non-RCT studies also provided new evidence that had become available since the publication of the previous appraisal of ruxolitinib. The Committee discussed the relationship between the marketing authorisation for ruxolitinib and the populations in the COMFORT trials and the 4 non-RCT studies. The Committee noted that the COMFORT trials included only patients who had intermediate-2 risk or high-risk myelofibrosis with platelet counts over $100x10^9$/L, 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 between 50–$100x10^9$/L and noted that these studies provided some evidence for the use of ruxolitinib in a subgroup of patients that were not included in the COMFORT trials but are included in the marking authorisation for ruxolitinib. The Committee concluded that data from the COMFORT trials and the 4 non-RCT studies should be considered, as the data were obtained from populations which are covered by the marketing authorisation for ruxolitinib and therefore 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 therefore the Committee would use the other studies principally as corroborative evidence.

4.4 The Committee considered the generalisability of the results from the COMFORT trials and the 4 non-RCT studies. The Committee heard from the clinical experts that ruxolitinib would mostly be used in higher-risk patients who had splenomegaly or symptoms. The Committee was also aware that the COMFORT trials did not include patients with low platelet counts (under $100x10^9$/L) but that 2 of the non-RCT studies (study 258 and EXPAND) included patients with platelet counts of between 50 and $100x10^9$/L. The Committee heard from the clinical expert that clinicians would treat patients with a platelet count of more than $100x10^9$/L with ruxolitinib (which is reflective of the population in the COMFORT trials) and also patients with a platelet count of between 50–$100x10^9$/L (which is reflective of the population in study 258 and EXPAND) as this is consistent with the summary of product characteristics for ruxolitinib. The clinical experts stated that clinicians may occasionally treat patients with platelet counts below $50x10^9$/L after careful consideration and informed discussion with the patient about the benefits and risks of ruxolitinib as 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 patients who would be treated with ruxolitinib in UK clinical practice; that is, those with intermediate-2 or high-risk myelofibrosis or with platelet counts of between 50–$100x10^9$/L or $100x10^9$/L or more.

4.5 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 treatment) was relevant to clinical practice in England. The Committee noted the Evidence Review Group's (ERG) concerns that the selection of treatments which made up 'best available therapy' in COMFORT-II included lenalidamide. The Committee

heard from the clinical experts that lenalidomide is rarely used in clinical practice in England. The Committee heard that hydroxycarbamide was the main treatment currently used in clinical practice, but patients with myelofibrosis are a heterogeneous group and therefore treatments would be frequently tailored to individual patient needs. The Committee concluded that the treatments used in the 'best available treatment' group in COMFORT-II were clinically relevant and that the comparator group also should be considered without lenalidomide.

4.6 The Committee considered the clinical-effectiveness evidence for ruxolitinib on spleen size and spleen volume. It noted that the COMFORT trials demonstrated that ruxolitinib provided significant benefits in terms of spleen size reduction and spleen volume reduction. 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 patient could have a modest size spleen with severe symptoms or a large spleen with minimal symptoms. The Committee noted that COMFORT-I also assessed symptom reduction, and that the results showed a clinically meaningful improvement in myelofibrosis associated symptoms for patients treated with ruxolitinib compared with a worsening of symptoms for patients treated with placebo. The Committee was aware that the results from 2 of the non-RCT studies (ROBUST and JUMP) also demonstrated 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 were low). The Committee was aware of the emphasis that 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 patients with intermediate-1, intermediate-2 and high-risk myelofibrosis. The Committee agreed that ruxolitinib had been shown to reduce spleen size and volume, and symptoms associated with myelofibrosis. It therefore concluded that ruxolitinib was a clinically effective treatment for disease-related splenomegaly or symptoms in adults with myelofibrosis.

4.7 The Committee considered the overall survival data. The Committee 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, (see section 3.11) were strongly indicative of a survival benefit for ruxolitinib. The Committee therefore concluded that there was sufficient evidence to show that ruxolitinib increased overall survival compared with 'best available therapy'.

4.8 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. The Committee 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 the management of myelofibrosis. The Committee 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 patients with myelofibrosis, but agreed that these were manageable.

Cost effectiveness

4.9 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 marking 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.

4.10 The Committee considered the costs that were incorporated into the company's economic model. The Committee noted that costs associated with lenalidomide had been incorporated into the company's economic model and its cost-effectiveness analyses, through its inclusion in the selection of therapies which made up 'best available care'. The Committee also noted that the ERG had provided exploratory analyses which excluded lenalidomide from the selection of therapies, and having heard from the clinical

experts that lenalidomide is rarely used in clinical practice, the Committee agreed that exploratory analyses presented by the ERG which excluded lenalidomide from the selection of therapies for 'best available therapy' were more representative of clinical practice in England. The Committee discussed whether the company's assumption of no drug wastage for ruxolitinib was appropriate. The Committee noted that the ERG had provided exploratory analyses 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. The Committee 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 treated with ruxolitinib used in the economic model reflected the drug costs for ruxolitinib in clinical practice. The Committee was aware that the drug costs for patients treated with 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 as the dosage used varied between patients and depended on a number of factors such as platelet count, response to treatment and adverse events. The Committee agreed that there was some uncertainty 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 as they were based on the same trial data from which the effectiveness inputs were based.

4.11 The Committee considered the most plausible incremental cost effectiveness ratio (ICER) for patients with intermediate-2 or high--risk myelofibrosis. The Committee discussed the company's and

ERG's cost-effectiveness analyses that included the patient access scheme for ruxolitinib. The Committee noted the company's base-case cost-effectiveness estimate for ruxolitinib compared with 'best available therapy' of £44,900 per quality-adjusted life year (QALY) gained and that neither the company's one-way sensitivity analyses or its scenario analyses resulted in an ICER for ruxolitinib greater than £50,000 per QALY gained. The Committee also noted the results of the ERG's exploratory analysis which produced ICERs ranging from £44,800 to £52,000 per QALY gained. The Committee was aware that preferred ERG exploratory analyses that excluded lenalidomide from the selection of therapies which made up 'best available therapy resulted in an ICER for ruxolitinib of £45,000 per QALY gained (see sections 3.51 to 3.53). The Committee agreed that the estimated ICER for ruxolitinib was largely robust to a range of values and model assumptions and concluded that the most plausible ICER for patients with intermediate--2 or high-risk myelofibrosis was in the region of £45,000 per QALY gained.

4.12 Because the ICER for patients with the intermediate--2 or 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.

4.13 The Committee discussed the criteria of small patient population. It accepted the estimates in the company's submission that 1185 patients 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 7000 and that ruxolitinib met the end-of-life criterion for a small patient population.

4.14 The Committee discussed the criteria 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.

4.15 The Committee discussed whether patients 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 intermediate-2 and high-risk disease from the various prognostic scoring systems (International Prognostic Scoring System for Primary myelofibrosis [IPPS], 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 patients with high-risk disease and a median of 2.9 to 4 years for patients with intermediate--2 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 as the data was based on patients before they had had any treatment. The Committee considered whether the life expectancy of patients with intermediate--2 risk myelofibrosis met the end-of-life criterion of less than 24 months and was not persuaded that the life expectancy for people with intermediate--2 risk myelofibrosis had been shown to be less than 24 months. The Committee concluded that it had not been provided with evidence that intermediate--2 risk patients had a life expectancy of less than 24 months and therefore did not meet all of the end-of life- criteria. 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. The Committee therefore concluded that it had been provided with evidence that high-risk patients met all of the end-of-life criteria.

4.16 The Committee considered whether ruxolitinib is an innovative treatment. The Committee agreed that ruxolitinib provided a step

change in treating splenomegaly and symptoms in patients 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 however there were no additional gains in health-related quality of life over those already included in the QALY calculations.

4.17 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

TAXXX	**Appraisal title:**	**Section**
Key conclusion		
Ruxolitinib is recommended as an option for treating disease-related splenomegaly or symptoms in adults with myelofibrosis, only in: • people with high-risk disease and • if the company provides ruxolitinib with the discount agreed in the patient access scheme. The Committee concluded that the most plausible incremental cost		1.1

effectiveness ratio (ICER) for patients with intermediate-2 or high-risk myelofibrosis was in the region of £45,000 per quality-adjusted life year (QALY) gained. Because the ICER for patients with the intermediate--2 or 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 not been provided with evidence that intermediate--2 risk patients met all of the end-of life- criteria. The Committee concluded that it had been provided with evidence that high-risk patients met all of the end-of-life criteria.		4.11 4.12 and 4.15
Current practice		
Clinical need of patients, including the availability of alternative treatments	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 be greatly beneficial to the wellbeing of people with myelofibrosis and their families.	4.1
The technology		

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 technology appraisal guidance 289 which was published in June 2013 Ruxolitinib is currently available through the cancer drug fund, as NICE Technology appraisal guidance 289 does not recommend ruxolitinib for the treatment of myelofibrosis. The Committee was aware from the clinical experts that clinicians considered ruxolitinib to be superior to hydroxycarbamide (among other best available therapies) for symptom control in myelofibrosis patients needing treatment.	4.2

What is the position of the treatment in the pathway of care for the condition?	The Committee was aware that the BCSH 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 discontinue 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 regarding the 24-week stopping rule was consistent with the treatment 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.	4.8
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The Committee 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 risk or high-risk myelofibrosis as its main source of evidence and supportive evidence from 4 non-	4.3

	randomised controlled trials (RCT) of ruxolitinib in patients with intermediate-risk myelofibrosis or a low platelet count (ROBUST, JUMP, study 258 and EXPAND). The Committee was aware that the COMFORT trials had been the main source of evidence for NICE's previous appraisal of ruxolitinib (TA289) but that longer term data from these trials had become available since the publication of the previous appraisal of ruxolitinib. The Committee was also aware that the 4 non-RCT studies also provided new evidence that had become available since the publication of the previous appraisal of ruxolitinib. The Committee concluded that data from the COMFORT trials and the 4 non-RCT studies should be considered, as the data were obtained from populations which are covered by the marketing authorisation for ruxolitinib and therefore 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 would use the other studies principally as corroborative evidence	

Relevance to general clinical practice in the NHS	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 treatment) was relevant to clinical practice in England. The Committee concluded that the results from the COMFORT trials and the non-RCTs were generalisable to the patients who would be treated with ruxolitinib in UK clinical practice; that is, those with intermediate-2 or high-risk myelofibrosis or with platelet counts of between 50–100x10^9/L or 100x10^9/L or more.	4.5 4.4
Uncertainties generated by the evidence	None identified	
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	None identified	

Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee agreed that ruxolitinib had been shown to reduce spleen size and volume, and symptoms associated with myelofibrosis. It therefore concluded that ruxolitinib was a clinically effective treatment for disease-related splenomegaly or symptoms in adults with myelofibrosis The Committee considered the overall survival data. The Committee 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 were strongly indicative of a survival benefit for ruxolitinib.	4.6 4.7
For reviews (except rapid reviews): How has the new clinical evidence that has emerged since the original appraisal (TAXXX) influenced the current (preliminary) recommendations?	Ruxolitinib is now recommended as an option for treating disease-related splenomegaly or symptoms in adults with myelofibrosis, in: people with high-risk disease. Longer term overall survival data (COMFORT--I median follow up 3 years, COMFORT--II median follow up 3.5 years) had become available since the publication of the previous appraisal of ruxolitinib.	4.3
Evidence for cost effectiveness		

Availability and nature of evidence	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 marking 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 only..	4.9
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee agreed that there was some uncertainty as to whether the drug costs for ruxolitinib used in the economic model reflected the drug costs for ruxolitinib in clinical practice. It agreed that the drug costs used were appropriate as they were based on the same trial data from which the effectiveness inputs were based.	4.10

Incorporation of health-related quality-of-life benefits and utility values 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?	No issues identified The Committee concluded that there were no additional gains in health-related quality of life over those already included in the QALY calculations.	 4.16
Are there specific groups of people for whom the technology is particularly cost effective?	None were identified.	
What are the key drivers of cost effectiveness?	The Committee agreed that the estimated ICER for ruxolitinib was largely robust to a range of values and assumptions made to the model	4.11

Most likely cost-effectiveness estimate (given as an ICER)	The Committee concluded that the most plausible ICER for patients with intermediate--2 or high-risk myelofibrosis was in the region of £45,000 per QALY gained.	4.11
For reviews (except rapid reviews): How has the new cost-effectiveness evidence that has emerged since the original appraisal (TAXXX) influenced the current (preliminary) recommendations?	With the patient access scheme included, ruxolitinib was now considered to be a cost effective use of NHS resources for people with high-risk myelofibrosis,.	
Additional factors taken into account		
Patient access schemes (PPRS)	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.	2.3

End-of-life considerations	The Committee concluded that the eligible population for England did not exceed 7000 and that ruxolitinib met the end-of-life criterion for a small patient population. The Committee concluded that treatment with ruxolitinib provided an extension of life of more than an average of 3 months. The Committee considered whether the life expectancy of patients with intermediate--2 risk myelofibrosis met the end-of-life criterion of less than 24 months and was not persuaded that the life expectancy for people with intermediate--2 risk myelofibrosis had been shown to be less than 24 months. 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.	4.13 4.14 4.15 4.15
Equalities considerations and social value judgements	No equalities issues were identified.	

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 hhave 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 [NICE to add details at time of publication]

5.5 NICE has developed tools [link to www.nice.org.uk/guidance/TAXXX] to help organisations put this guidance into practice (listed below). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Related NICE guidance

Details are correct at the time of consultation and will be removed when the final guidance is published. Further information is available on the NICE website.

- **Published**
- 'Ruxolitinib for disease-related splenomegaly or symptoms in adults with myelofibrosis' NICE Technology appraisal guidance 289 (2013). (http://www.nice.org.uk/guidance/ta289)

7 Proposed date for review of guidance

7.1 NICE proposes that the guidance on this technology is considered for review by the Guidance Executive 3 years after publication of the guidance.NICE welcomes comment on this proposed date. 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 Stevens

Chair, Appraisal Committee

October 2015

8 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

Gail Coster
Advanced Practice Sonographer, Mid Yorkshire Hospitals NHS Trust

Professor Peter Crome
Honorary Professor, Dept 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 Iain Miller
Founder & CEO, Health Strategies Group

Professor Stephen O'Brien
Professor of Haematology, Newcastle University

Dr Anna O'Neill
Deputy Head of Nursing & 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

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
Technical Lead

Nicola Hay
Technical Adviser

Lori Farrar
Project Manager

9 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by Centre for reviews and dissemination and centre for health economics, York:

- Hodgson R, Wade R, Biswas M, Harden M, Woolacott N. Ruxolitinib for disease-related splenomegaly or symptoms in adults with myelofibrosis (review of TA289): A Single Technology Appraisal. CRD and CHE Technology Assessment Group, 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 CCG
- NHS South Norfolk CCG
- 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 Ruxolitinib for disease-related splenomegaly or symptoms in adults with myelofibrosis (review of TA289) by attending the initial Committee discussion and providing a written statement to the Committee. They are invited to comment on the ACD.

- Professor Claire Harrison, Consultant Haematologist, nominated by the Royal College of Pathologists – clinical expert
- Dr Tim Somervaille, Honorary consultation 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