NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Ruxolitinib for treating acute graft versus host disease that responds inadequately to corticosteroids in people 12 years and over

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

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation 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 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 age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: November 2024

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 evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using ruxolitinib in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 10 January 2025
- Second evaluation committee meeting: 12 February 2025
- Details of the evaluation committee are given in section 4

1 Recommendations

1.1 Ruxolitinib is not recommended, within its marketing authorisation, for treating acute graft versus host disease that has an inadequate response to corticosteroids in people 12 years and over.

1.2 This recommendation is not intended to affect treatment with ruxolitinib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop. For young people (less than 18 years), this decision should be made jointly by the healthcare professional, the young person, and their parents or carers.

Why the committee made these recommendations

Standard care for acute graft versus host disease (GvHD) is corticosteroids. If corticosteroids have not worked well enough, subsequent treatments can include extracorporeal photopheresis, mycophenolate mofetil, etanercept and infliximab. Ruxolitinib is an alternative to these second-line treatments.

Clinical trial evidence shows that acute GvHD is more likely to improve with ruxolitinib than with standard care. People who have ruxolitinib are also less likely to need another treatment, have a relapse of their underlying disease, or die. But, this is uncertain because of the design of the trials.

There are uncertainties in the economic evidence. This is because of assumptions used by the company in its economic model. These include the total costs incurred with ruxolitinib and the quality of life of people who develop chronic GvHD. Because of these uncertainties, it is not possible to determine the most likely cost-effectiveness estimates for ruxolitinib. So, more analyses are needed, and ruxolitinib is not recommended.

2 Information about ruxolitinib

Marketing authorisation indication

2.1 Ruxolitinib (Jakavi, Novartis) is indicated for 'the treatment of patients aged 12 years and older with acute graft versus host disease who have inadequate response to corticosteroids'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for ruxolitinib.

Price

2.3 The list price for a 56-tablet pack of 5 mg ruxolitinib is £1,428, and for a 56-tablet pack of 10 mg ruxolitinib is £2,856 (excluding VAT; BNF online, accessed November 2024).

2.4 The company has a commercial arrangement. This makes ruxolitinib available to the NHS with a discount and it would have also applied to this indication if the technology had been recommended. The size of the discount is commercial in confidence.

3 Committee discussion

The evaluation committee considered evidence submitted by Novartis, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

3.1 Graft versus host disease (GvHD) can occur after an allogeneic haematopoietic stem cell transplant (HSCT), when donated white blood cells (T cells) attack the body's own cells. Allogeneic HSCT is used as a treatment for some blood cancers, but may also be used for non-cancerous conditions. GvHD can be acute or chronic, differentiated by clinical manifestations, diagnostic criteria and pathology. Acute GvHD

typically affects the skin, liver and gastrointestinal tract, whereas chronic GvHD can affect any organ. The patient experts explained that the skin rash associated with acute GvHD can cover large areas of the body, and can make contact with clothes, bedsheets and furniture exceptionally painful. They described tongue lesions that prevent speaking or eating normally, and bouts of diarrhoea that cause weight loss and fatigue. They emphasised that acute GvHD has a significant impact on a person's independence and mental health. The patient experts also described the burden on carers. People with acute GvHD can require 24-hour care because of the severity of the condition. This, coupled with frequent and prolonged hospital stays, can strain relationships. The committee concluded that acute GvHD had a considerable impact on people with the condition and their carers.

Clinical management

Treatment options and unmet need

3.2 The company positioned ruxolitinib as an alternative to the treatments that are currently used in NHS practice for corticosteroid-refractory acute GvHD. NHS England's clinical commissioning policy on treatments for graft versus host disease following haematopoietic stem cell transplantation (PDF only) was issued in 2017. It recommends that people with moderate, severe or very severe acute GvHD (grades 2 to 4) should be treated first with systemic corticosteroids. For acute GvHD that is refractory to corticosteroids, the policy recommends treatment with extracorporeal photopheresis (ECP), a blood-filtering procedure in which white blood cells are collected, treated with a light-activated drug, exposed to ultraviolet light, and returned to the body. The clinical experts noted that ECP is the most common treatment for corticosteroid-refractory acute GvHD in the NHS. But, practice varies, and clinicians use a variety of treatments, many of which are unlicensed for treating acute GvHD. The clinical experts noted that some of this variation is driven by issues with accessing ECP. ECP is available at a few therapeutic apheresis services

and a limited number of hospital trusts. The patient experts explained that some people must commit significant time and money to travel for treatment, require invasive venous access, and often have long hospital stays. They also noted that other available treatments have many limitations. For example, immunosuppressants, such as corticosteroids, can cause a range of adverse effects that reduce quality of life, including an increased risk of infections and diabetes. Because people with acute GvHD have suppressed immunity, they are already prone to frequent infections and may require admission to hospital. To prevent this, they may need to isolate, which further impairs their quality of life. The patient experts described how much they would value ruxolitinib because, as an oral treatment, it may be able to be taken at home. This may also reduce infection risk. The committee concluded that the current treatment for acute GvHD has many limitations for clinicians and people with the disease, there is a substantial unmet need for new treatments, and ruxolitinib could address some of these issues.

Clinical effectiveness

Data sources in acute GvHD

3.3 The clinical-effectiveness evidence for ruxolitinib for acute GvHD came from 2 trials: REACH1 and REACH2. REACH1 was a US-based single-arm phase 2 study of ruxolitinib. REACH2 was a phase 3 randomised, controlled, open-label, superiority trial that compared ruxolitinib with the investigator's choice of standard care. It was done across 22 countries, including the UK. Both REACH1 and REACH2 included people 12 years and over with corticosteroid-refractory acute GvHD following an allogeneic HSCT. In REACH2, 154 people were randomised to ruxolitinib 10 mg twice daily and 155 people were randomised to standard care (see section 3.5 for a discussion on the generalisability of the standard-care treatments). The committee concluded that the randomised trial (REACH2) was important for decision making, but that the uncontrolled trial (REACH1) was not.

The primary outcome of REACH2 was overall response rate at day 28, defined as the proportion of people who had a complete response (score of 0 for grading in all evaluable organs) or partial response (improvement of 1 stage in 1 or more organs). The overall response rate at day 28 was higher with ruxolitinib than with standard care (62.3% compared with 39.4%; odds ratio 2.64, 95% confidence interval 1.65 to 4.22, p<0.0001). People allocated to ruxolitinib also had longer failure-free survival (secondary endpoint) than people allocated to standard care (4.86 compared with 1.02 months; hazard ratio 0.51, 95% confidence interval 0.39 to 0.66, p<0.0001). Failure-free survival was defined as the time from the date of randomisation to the date of haematological disease relapse or progression, non-relapse mortality, or start of a new systemic acute GvHD treatment. There was no statistically significant difference in overall survival (secondary endpoint) between the treatment groups (hazard ratio 0.85, 95% confidence interval 0.63 to 1.14, p=0.28).

The committee queried the company's interpretation of the failure-free survival outcome, noting that its definition meant that failure included starting a new systemic treatment. The committee understood that REACH2 had an open-label design, where both participants and investigators knew which treatment people were allocated to. It also noted that people allocated to standard care were able to switch to ruxolitinib from day 28 of treatment. The committee was concerned that people may have perceived ruxolitinib as a more effective or more desirable (being a tablet) treatment. So, more people in the standard-care arm may have chosen to switch than might have been expected, inflating the number of treatment failures. The company responded that it had statistically adjusted its estimates of effectiveness related to time to relapse, chronic GvHD, and death for crossover, but could not adjust for crossover in failure-free survival. The committee agreed that this uncertainty could not be resolved with the available data, but it would account for this in its decision making. The committee concluded that REACH2 demonstrated that ruxolitinib was an effective treatment for acute GvHD, but the trial

design and definition of outcomes meant that there was inherent uncertainty in its results.

Evidence for young people and grade 1 acute GvHD

3.4 The marketing authorisation for ruxolitinib is for 'patients aged 12 years and older with acute graft versus host disease who have inadequate response to corticosteroids'. The EAG noted that only 3% of people in REACH2 were 12 to 17 years, and that its eligibility criteria did not include people with grade 1 acute GvHD. So, REACH2 did not capture these populations. The company referred to advice from clinicians, who suggested there was no difference between adults and young people in acute GvHD manifestation, pathophysiology or treatment options. The clinical experts in the meeting agreed with the company that they would expect little difference between young people and older people in disease manifestations or outcomes, or in the magnitude of effectiveness when using ruxolitinib compared with standard care. The company also noted that the option for treating grade 1 disease was essential for people who are at high risk of developing disease at a severity of grade 2 or higher. The committee concluded that although REACH2 did not capture these populations, it was satisfied that its recommendations were generalisable to young people.

Generalisability of standard care

3.5 The standard-care arm of REACH2 permitted healthcare professionals and participants to choose the treatment. The EAG questioned whether the standard-care treatments used in REACH2 reflected NHS practice. The clinical experts noted that ECP was the preferred treatment in the NHS and would be used in practice in more people than in REACH2 (where 27% of people had it). They explained that ECP is preferred because of higher perceived efficacy, a lack of good evidence for the other comparator treatments, and the NHS clinical commissioning policy (see section 3.2), which allows ECP to be funded more easily than other treatments. The EAG highlighted that the different standard-care

treatments may have different levels of efficacy. So, if ECP is the most effective treatment (as could be inferred by the NHS preference for its use) and was used by a higher proportion of people in NHS practice than in REACH2, then REACH2 may have underestimated standard-care efficacy. The company explained that it did not have the data to conduct subgroup analyses for all standard-care treatments, and that such analyses would break randomisation. The company referred to failure-free and overall survival curves from REACH2 that showed similar outcomes between ECP and the other standard-care treatments. The clinical experts also highlighted that it is difficult to decide that one treatment is more effective than another. This is because of differences between individuals in the trial and variations in treatment protocols in different countries. The committee concluded that it had not been presented with convincing evidence that ECP is more effective than other standard-care treatments. It noted that this uncertainty could not be resolved with the available data and should be accounted for in its decision making. So, although the committee cautioned that a lack of data did not imply a lack of difference between the treatments, it accepted that the results of REACH2 could be generalised to the NHS.

Data source in chronic GvHD

3.6 The company used clinical evidence from REACH3 to inform the chronic GvHD health states in the model, acknowledging that some people with acute GvHD go on to develop chronic GvHD. REACH3 was a phase 3 randomised, open-label, multicentre trial. It compared ruxolitinib 10 mg twice daily with the investigator's choice of standard care. It included people who had had an allogeneic HSCT, were 12 years and over, and had moderate or severe corticosteroid-refractory chronic GvHD. It was done across 28 countries, including the UK. The trial allowed people in the standard-care arm to switch to ruxolitinib at or after week 24 if they did not have or maintain a complete or partial response, had adverse effects from a control treatment, or had a flare-up of their chronic GvHD. The committee noted that 38% of people in the standard-care arm switched to

ruxolitinib at or after week 24. Because ruxolitinib was effective relative to standard care, the committee concluded that this crossover would probably have had a large impact on the clinical outcomes measured in the trial for standard care of chronic GvHD.

Economic model

Company's modelling approach

3.7 To estimate the cost-effectiveness of ruxolitinib, the company simulated the treatment of NHS patients with acute GvHD with either ruxolitinib or standard care over a lifetime time horizon. The company's model was a state-transition model containing 7 mutually exclusive health states:

- 'Failure-free': the starting health state. People remain in the failure-free health state until they start a new systemic treatment for acute GvHD, have a relapse of their underlying haematological disease, experience non-relapse mortality, or develop chronic GvHD.
- 'Relapse': people have a relapse of their underlying haematological disease.
- 'New systemic treatment': people start a new systemic treatment for acute GvHD.
- 'Chronic GvHD – failure-free': people develop chronic GvHD and remain in this health state until they have a new systemic chronic GvHD therapy or have a relapse of their underlying haematological disease.
- 'Chronic GvHD – relapse': people have chronic GvHD and a relapse of their underlying haematological disease.
- 'Chronic GvHD – new systemic treatment': people start a new systemic treatment for chronic GvHD.
- 'Death': the absorbing state which people can enter from any health state.

Simulated people with corticosteroid-refractory acute GvHD enter the model in the failure-free health state and have either ruxolitinib or

standard care. People transition between the different acute GvHD health states using transition probabilities that the company estimated from time-to-event outcomes in REACH2. The company assumed that only the transitions from the 'failure-free' state differed between ruxolitinib and standard care. Other transition probabilities, from the 'new systemic treatment' and 'relapse' health states to other states, were assumed by the company to be the same for ruxolitinib and standard care and were estimated using REACH2 data pooled across both treatment arms. For the chronic GvHD health states, the company estimated transition probabilities from the standard-care arm of REACH3.

The EAG noted that the model structure did not capture response to treatment. It stated that the 'failure-free' health state contained people who had a treatment response and no symptoms, and people who did not have a treatment response and had ongoing symptoms, but had not yet transitioned to another health state. The EAG reasoned that these subgroups would have very different outcomes and utility. The EAG noted that REACH2 showed an increase in average utility of people in REACH2 in failure-free survival after 4 weeks, which may have been because people without a treatment response transitioned to other health states. The committee questioned why the model was designed around failure-free survival, a secondary endpoint in REACH2, rather than the primary outcome of overall response. It also recalled its discussions in section 3.3 that treatment failure may have been inflated in the standard-care arm because of crossover. The company explained that response outcomes would add uncertainty to its model. It cited NICE's technology appraisal guidance on belumosudil for chronic GvHD, in which clinical advice stated that failure-free survival is a more clinically relevant outcome than response. Also, the clinical experts at the meeting explained that response is difficult to define and can vary in such a heterogeneous population.

In response, the committee noted that the technology appraisal committee on belumosudil for chronic GvHD concluded that the model it had been presented with was not the most appropriate approach. But, the committee highlighted that it was not a true response-based model, and instead used response to split the failure-free survival health state. The committee appraising ruxolitinib also highlighted that acute GvHD and chronic GvHD are different conditions. So, a response-based model for acute GvHD may be more appropriate than one based on failure-free survival, and may have reduced some of the model's complexity. The committee was not convinced that the current model had the appropriate structure and agreed that the current structure created significant uncertainties. But, on balance, it concluded that it was likely to be acceptable if the company addressed other issues with the modelling assumptions, and if the committee accounted for the uncertainty in its decision-making.

Standard care used in the model

3.8 The company adjusted the proportion of people having each treatment in the standard-care arm of REACH2 to reflect the likely standard-care costs in the NHS. Clinical advice sought by the company suggested that in the NHS, relative to the trial, more people would have ECP, and that antithymocyte globulin, everolimus and low-dose methotrexate were not used at second line. Table 1 shows the revised treatment proportions used in the company's model.

Table 1 Revised treatment proportions in the company's model

Treatment	Proportion of people in REACH2 (%)	Proportion of people in the company's model (%)
ECP	27	45
Mycophenolate mofetil	17	17
Etanercept	15	15
Antithymocyte globulin	13	0
Infliximab	11	15
Mesenchymal stromal cells	10	5
Low-dose methotrexate	3	0
Sirolimus	2	1
Everolimus	1	0
No treatment	3	3

The EAG explained that adjusting the model to reflect the proportion of treatments used in the NHS is important, because the model would then capture the cost of each treatment. The EAG recalled its comments in section 3.5 that different standard-care treatments may have different levels of efficacy for acute GvHD. It also noted that ECP is expensive relative to the other standard-care treatments. So, by increasing the proportion of people in the model on ECP, the company had increased the costs incurred in the standard-care arm but had not increased the efficacy. This may have biased the model in favour of ruxolitinib. The committee recalled the arguments made by the company in section 3.5 that data from REACH2 showed similar outcomes between the standard-care components. It also recalled the statements from the clinical experts that, with the available evidence, it was difficult to determine whether one standard-care treatment was better than another. The committee concluded that it was appropriate for the company to adjust only the costs of standard care in the model. But, it recognised that this was another source of uncertainty that it would account for in its decision making.

Time-to-event extrapolations

3.9 The company used time-to-event data from REACH2 to estimate the transition probabilities from the 'failure-free' acute GvHD health state to 'new systemic treatment for acute GvHD', 'relapse of underlying haematological disease', 'chronic GvHD' and 'death'. It fitted models to the time-to-event data for failure-free to new systemic treatment, failure-free to relapse, failure-free to chronic GvHD, and failure-free to death. The company chose to fit joint models where there was evidence of proportional hazards, and independent curves where there was not. Joint models apply a single distribution to both treatment arms, whereas independent models fit a separate distribution to each arm. The company chose curves based on statistical goodness-of-fit, clinical plausibility and visual inspection. The EAG disagreed with the company's model fitting. It noted the choice of joint models was inappropriate for failure-free to relapse and failure-free to death because the proportional hazards assumption was not met. It also noted that the curves did not fit well to the underlying Kaplan–Meier data. Because of this uncertainty, the EAG assumed that the only benefit of ruxolitinib was in reducing the risk of moving from the 'failure-free' to 'new systemic treatment' health states. All other curves were based on pooled ruxolitinib and standard-care data, and the transition probabilities were the same for both arms. The committee noted that this counterintuitively decreased the incremental cost-effectiveness ratio (ICER). The EAG explained that this was because fewer people would enter the costly chronic GvHD health state. So, although both the incremental quality-adjusted life years (QALYs) and incremental costs decreased, the incremental costs decreased proportionally more, making ruxolitinib more cost-effective than it would have been otherwise.

The committee questioned the company's approach of assuming that ruxolitinib would improve time to relapse and time to death. The committee recalled the results for overall survival of REACH2 (see section 3.3). It also reasoned that it was implausible that ruxolitinib would affect the recurrence of a person's underlying haematological condition (the

condition for which they had a HSCT). The clinical experts noted that ruxolitinib would not have a significant effect on time to relapse. The committee also reiterated its concerns over the open-label design of REACH2 (see section 3.3) and how this could have affected time to new systemic treatment. Overall, the committee agreed that there was substantial uncertainty in the time-to-event data. It concluded that the EAG's assumptions were preferred where the likely treatment benefit of ruxolitinib was only in delaying the time to new systemic treatment.

Treatments after ruxolitinib or standard care

3.10 In the model, people who enter the health state reflecting a new systemic treatment incur a treatment cost. The company calculated the proportion of people having each subsequent treatment from the pooled ruxolitinib and standard-care arms in REACH2 (table 2).

Table 2 Proportion of people having subsequent treatment in the company's model

Treatment	Proportion of people (%)
Mycophenolate mofetil	21
ECP	16
Etanercept	19
Mesenchymal stromal cells	11
Antithymocyte globulin	10
Infliximab	7
Sirolimus	2
Low-dose methotrexate	1
Everolimus	1

The committee noted that the distributions of subsequent treatment were the same for people who initially had ruxolitinib and those who initially had standard care. It reasoned that people who initially had ruxolitinib would be more likely to then have ECP than people who had standard care. This is because people in the NHS who have ruxolitinib still have the option of subsequent ECP, whereas about half of people who have standard care

have ECP initially and would not usually be retreated with ECP if they require further treatment. This may increase the costs of subsequent treatment in the ruxolitinib arm. To see the impact of this on the ICER, the committee requested that the company update its model so that the distribution of subsequent treatments after ruxolitinib better reflects the treatment distribution that would be given in practice, if ruxolitinib was made available.

Modelled chronic GvHD and REACH3

3.11 The company modelled chronic GvHD transition probabilities using data from the standard-care arm of REACH3. The EAG noted that only 10.4% of people in REACH3 had corticosteroid-refractory acute GvHD before they developed chronic GvHD and entered REACH3. But, the company's model implicitly assumed that everyone who entered the chronic GvHD health state previously had corticosteroid-refractory acute GvHD. The EAG questioned whether the clinical characteristics and outcomes would be different between people who did and did not have corticosteroid-refractory acute GvHD before developing chronic GvHD. The clinical experts explained that they would expect little difference in outcomes between people whose acute GvHD resolved before chronic GvHD and people who did not have acute GvHD before chronic GvHD. But, they explained that people who developed chronic GvHD while they still had unresolved acute GvHD may have more severe disease and experience worse outcomes. The company cited data from REACH3 that showed no difference in failure-free survival between people with chronic GvHD who did and did not have previous acute GvHD. The committee concluded that, on balance, the data from REACH3 was a reasonable proxy for modelling the chronic GvHD health states. But, it recognised that this was another source of uncertainty that could not be resolved.

Utility values

Estimating utility values

3.12 To estimate utility values for the health states, the company fitted a model to pooled EQ-5D data from REACH2 and REACH3. The company noted a substantial increase in utility for people in the acute GvHD 'failure-free' health state after 4 model cycles (112 days). The company added a covariate to its model to account for this. The EAG had issues with the company's utility values. First, the EAG thought that it was inappropriate to pool the utility values from REACH2 and REACH3, given that the populations differed. In response, the company provided models based on separate data. Second, the EAG noted that simulated people who transitioned from the 'failure-free' health state to the 'chronic GvHD – failure-free' health state in the first 4 model cycles experienced a significant utility increase. The EAG thought that this was unlikely, because people who transition in the first 4 cycles are more likely to still be experiencing acute GvHD symptoms alongside developing chronic GvHD. Third, the EAG was concerned that the utility value for people in the 'failure-free' health state after 4 model cycles was significantly higher than the utility value used in the company's previous submissions to other health technology assessment agencies in Canada and Australia, although the EAG noted that these submissions used models with different structures. So, for its base case, the EAG changed the utility value in the 'chronic GvHD – failure-free, first 4 cycles' to be the same as the 'failure-free, first 4 cycles' value. The EAG also did scenarios using the utility models based on separate REACH2 or REACH3 data. The committee concluded that the adjustment to the 'failure-free, first 4 cycles' utility value was appropriate, but noted this change had little effect on the ICER.

Quality of life with chronic GvHD

3.13 The committee had concerns about the face validity of the utility values in the chronic GvHD health states. In particular, it noted that the utility value for the 'chronic GvHD – new systemic treatment' state was similar to the values for the 'failure-free acute GvHD' and 'chronic GvHD – failure-free' health states. It thought that this was implausible, given that people

typically experience worse quality of life with each subsequent line of treatment. The company explained that because people with chronic GvHD are managed as outpatients, the utility value could be relatively high. But, the committee concluded that the utility value for the 'chronic GvHD – new systemic treatment' was implausibly high and would probably worsen over time. Because people in the model generate most of their QALYs in the chronic GvHD health state, the committee thought that the model could be sensitive to changes in this utility. So, it requested that the company update its model using plausible and coherent utility values for the chronic GvHD health states that had face validity.

Costs

Treatment duration

3.14 The company calculated treatment duration, and associated costs, using the average proportion of people remaining on treatment at each week of REACH2, and their average dose of ruxolitinib. The committee questioned whether people in REACH2 who developed chronic GvHD continued having ruxolitinib. The company confirmed that some people did continue having ruxolitinib after developing chronic GvHD. The clinical experts noted that this aligned with NHS clinical practice. The committee asked if this was reflected in the model. The company confirmed that the treatment duration in the model was not linked to a health state. But, it added that because the treatment duration was calculated from REACH2, the model implicitly captured those people who continued ruxolitinib after developing chronic GvHD. The committee concluded that the modelled duration of treatment was appropriate and aligned with how ruxolitinib is likely to be used in NHS clinical practice.

Treatment wastage

3.15 The company's model assumed that there would be no wastage of ruxolitinib. The clinical experts noted that acute GvHD can be treated in hospital, with ruxolitinib dispensed by hospital pharmacies. But, there will

be some people with acute GvHD who are treated as outpatients. The committee agreed that the risk of wastage is higher among outpatients, and that wastage would increase the cost of ruxolitinib. The committee concluded that some ruxolitinib would be wasted and asked the company to update its model to include wastage of ruxolitinib.

Severity of acute GvHD

3.16 The committee discussed the severity of the condition (the future health lost by people living with the condition and having standard care in the NHS). The committee may apply a greater weight to QALYs (a severity modifier) if technologies are indicated for conditions with a high degree of severity. The company provided estimates of absolute and proportional QALY shortfalls in line with NICE's manual on health technology evaluation. Using the company's assumptions resulted in a severity weight of 1.2. The EAG's assumptions produced a similar estimate of absolute and proportional QALY shortfall, which also resulted in a severity weight of 1.2. The committee noted that even if the efficacy of standard care was underestimated in the model (section 3.5), this would be unlikely to change the resulting severity modifier. So, the committee concluded that the severity weight of 1.2 applied to the QALYs was likely to be appropriate, but this may be affected by updates to the model.

Other factors

Equality

3.17 The committee discussed that the risk of acute GvHD is increased when there is a genetic mismatch between donor and recipient. The company highlighted that finding a genetic match is particularly difficult for some ethnic groups, which may lead to an increased incidence of acute GvHD among these groups. The committee also recalled statements from the patient and clinical experts that there are access issues with ECP that may mean significant travel time, and associated costs, for patients and carers. The patient and clinical experts also highlighted equality issues

around access to ruxolitinib. First, they noted that ruxolitinib was commissioned in Scotland and Wales. Second, they explained that ruxolitinib was available in England during the COVID-19 pandemic through an NHS England rapid commissioning policy. This policy was withdrawn in 2022, but some people are still able to access ruxolitinib through individual funding requests or local approval from some hospital trusts. The committee acknowledged the concerns raised but concluded that they were not relevant equality considerations that could be addressed in its decision making in a technology appraisal.

Uncaptured benefits

3.18 The committee discussed whether there were any uncaptured benefits of ruxolitinib. It recalled statements from the patient and clinical experts that many people with acute GvHD would prefer ruxolitinib because it is an oral treatment. They noted that this would be particularly important for immunosuppressed people who could avoid hospital visits for ECP. The committee recognised that if ruxolitinib could permit people to gradually reduce their dose of corticosteroids, the corticosteroid-associated adverse effects would lessen relative to standard care. It also noted statements from carers about the all-encompassing nature of caring for a person with acute GvHD, and that the model does not include estimates of carer disutility. So, the committee concluded that there were uncaptured benefits of ruxolitinib and took these into account in its decision making.

Cost-effectiveness estimates

Acceptable ICER

3.19 NICE's manual on health technology evaluations notes that, above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other

aspects, including uncaptured health benefits. The committee noted the high level of uncertainty, specifically:

- The open-label design of the REACH2 and REACH3 trials may have affected the failure-free survival outcome in the standard-care arms of both trials (sections 3.3 and 3.6).
- Increasing the proportion of people having ECP in the standard-care arm increases the costs of standard care but does not change the efficacy. This may underestimate the standard-care treatment effect if different treatment options have different efficacies (sections 3.5 and 3.8).
- The company's model is structured around the failure-free survival outcome. This was a secondary outcome in REACH2. Failure-free survival was primarily driven by switching to new treatment and may have been affected by the open-label design (section 3.7).
- The distribution of follow-on treatments for acute GvHD would probably differ for people who initially had ruxolitinib and for people who initially had standard care (section 3.10).
- Chronic GvHD was modelled by the company using data from REACH3, but only some people in REACH3 had corticosteroid-refractory acute GvHD before chronic GvHD (section 3.11).
- The utility value for the 'chronic GvHD – new systemic treatment' seemed implausibly high (section 3.13).
- Wastage was not included in the company's model (section 3.15).

The committee was unable to identify a threshold because this would need to account for both the resolvable uncertainties in the analyses requested and the currently unresolvable uncertainties (section 3.20).

Cost-effectiveness estimates and further analyses

3.20 Because of confidential commercial arrangements for ruxolitinib, the comparators and other treatments in the model, the exact cost-effectiveness estimates are confidential and cannot be reported here.

Neither the company's nor the EAG's base-case ICERs included all the committee's preferred assumptions, so the ICERs based on the committee's preferred assumptions are unknown. The following preferred assumptions of the committee aligned with adjustments made by the EAG to form its base case:

- extrapolating survival by assuming treatment benefit of ruxolitinib for time to new systemic treatment only (section 3.9)
- lowering the utility value for the 'chronic GvHD – failure-free, first 4 cycles' health state (section 3.12)
- applying adverse event disutilities so that they are multiplicative.

The committee would like the company to update its model to include the following:

- different distribution of subsequent treatments for acute GvHD depending on whether previous treatment was ruxolitinib or standard care (section 3.10)
- scenarios varying the utility value for the 'chronic GvHD – new systemic treatment' health state (section 3.13)
- the expected cost of wastage of ruxolitinib (section 3.15).

Conclusion

Ruxolitinib is not recommended

3.21 The committee decided that the cost-effectiveness estimates presented by the company and EAG were uncertain because they did not include all the preferred assumptions. Given the uncertainty, the committee would like to see additional analyses. The committee agreed that it was possible the cost-effectiveness estimates were above the range that NICE considers a cost-effective use of NHS resources. So, the committee concluded that it could not recommend ruxolitinib for treating acute GvHD that has an inadequate response to corticosteroids in people 12 years and over.

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D. Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

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

Chair

Amanda Adler

Interim vice-chair, technology appraisal committee D

NICE project team

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

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Technical lead

Michelle Green

Technical adviser

Leena Issa

Project manager

Ian Watson

Associate director

ISBN: [to be added at publication]