# Single Technology Appraisal

# Ruxolitinib for treating acute graft versus host disease refractory to corticosteroids in people aged 12 and over (review of TA839) [ID6377]

# Committee Papers

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**SINGLE TECHNOLOGY APPRAISAL**

# Ruxolitinib for treating acute graft versus host disease refractory to corticosteroids in people aged 12 and over (review of TA839) [ID6377]

**Contents:**

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from Novartis**

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. Anthony Nolan
   b. NHS England
   c. Therakos

3. **Comments on the Draft Guidance from experts:**
   a. Dr Donal McLornan - clinical expert, nominated by Novartis

4. **External Assessment Group critique of company comments on the Draft Guidance**

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

NICE National Institute for Health and Care Excellence

**Ruxolitinib for treating acute graft versus host disease refractory to corticosteroids in people aged 12 and over (review of TA839) [ID6377]**

**Draft guidance comments form**

**Consultation on the draft guidance document – deadline for comments** 5pm on Friday 10 January 2025. Please submit via NICE Docs.

| | |
|---|---|
| | Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.<br><br>The Appraisal Committee is interested in receiving comments on the following:<br>• has all of the relevant evidence been taken into account?<br>• are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?<br>• are the provisional recommendations sound and a suitable basis for guidance to the NHS?<br><br>NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:<br>• could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology;<br>• could have any adverse impact on people with a particular disability or disabilities.<br><br>Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.** |
| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | Novartis Pharmaceuticals UK Limited |

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

**Ruxolitinib for treating acute graft versus host disease refractory to corticosteroids in people aged 12 and over (review of TA839) [ID6377]**

**Draft guidance comments form**

**Consultation on the draft guidance document – deadline for comments** 5pm on Friday 10 January 2025. Please submit via NICE Docs.

| | |
|---|---|
| **Disclosure**<br>Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.]<br>Please state:<br>• the name of the company<br>• the amount<br>• the purpose of funding including whether it related to a product mentioned in the stakeholder list<br>• whether it is ongoing or has ceased. | N/A |

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

**Ruxolitinib for treating acute graft versus host disease refractory to corticosteroids in people aged 12 and over (review of TA839) [ID6377]**

**Draft guidance comments form**

**Consultation on the draft guidance document – deadline for comments** 5pm on Friday 10 January 2025. Please submit via NICE Docs.

| | |
|---|---|
| Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | 1) Since April 2005, Novartis has exclusively licensed glycopyrronium bromide and certain intellectual property relating to its use and formulation from Vectura and its co-development partner, Sosei Heptares. The following inhaled medications are comprised of, or contain, glycopyrronium bromide:<br>- Seebri® Breezhaler® (glycopyrronium bromide), used as a maintenance treatment for Chronic Obstructive Pulmonary Disease (COPD)<br>- Ultibro® Breezhaler® (indacaterol/glycopyrronium bromide), used as a maintenance treatment for COPD<br>- Enerzair® Breezhaler® (indacaterol/glycopyrronium bromide/mometasone furoate), used as a maintenance treatment for asthma uncontrolled with long-acting beta-agonist (LABA)/inhaled corticosteroid (ICS).<br>Phillip Morris International (a tobacco company) has acquired Vectura Group Limited (formerly Vectura Group plc).<br>2) Novartis has been granted an exclusive license from Japan Tobacco Inc. (JT) under JT patents on a world-wide basis for commercial rights to trametinib (Mekinist®; TMT212). Trametinib is a kinase inhibitor indicated as a single agent or in combination with dabrafenib for the treatment of several oncology indications. In 2015, as part of its purchase of oncology products from GlaxoSmithKline, Novartis obtained the worldwide exclusive rights granted by JT to develop, manufacture, and commercialize trametinib. JT retains co-promotion rights in Japan |
| **Name of commentator person completing form:** | [redacted] [redacted] |

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

**Ruxolitinib for treating acute graft versus host disease refractory to corticosteroids in people aged 12 and over (review of TA839) [ID6377]**

**Draft guidance comments form**

**Consultation on the draft guidance document – deadline for comments** 5pm on Friday 10 January 2025. Please submit via NICE Docs.

## Background

Novartis would like to thank the committee for the opportunity to respond to the Draft Guidance Document (DGD) and to address the committee's concerns and uncertainties in this appraisal. Novartis are disappointed with the committee's provisional draft position not to recommend ruxolitinib for the treatment of steroid-refractory (SR) acute graft-versus-host-disease (aGvHD) (1). Novartis have updated the base case as per the committee's preferred assumptions, and hope that the additional analyses and information provided in this response will support the committee to provide a positive recommendation for ruxolitinib in patients with this condition.

Novartis welcome the committee's recognition of ruxolitinib as an effective treatment for SR-aGvHD (Section 3.3). The committee acknowledged that the current treatments for SR-aGvHD have many limitations for clinicians and people with the disease, including the time-consuming and financial aspect of having to travel to receive treatment, the increased risk of infection associated with travel and having to attend hospital appointments, and the range of associated side-effects which significantly impair patients' quality of life (QoL; Section 3.2). The committee concluded that there is a substantial unmet need for new treatments, and ruxolitinib could address some of these issues (Section 3.2). It must be emphasised that patient experts and clinical experts (2, 3) have described how the treatments currently available are of limited effectiveness, that access to them is variable and that the associated side-effects were often debilitating. Patients who were able to access ruxolitinib, either during the time of the COVID NHS England Rapid Commissioning Policy or through self-funding, described ruxolitinib as an effective and life-saving treatment, with very few side-effects compared with other treatments. If the initial decision remains unchanged, patients with SR-aGvHD will be denied access to an effective treatment option which increases overall response rate, increases failure-free survival, and improves QoL when compared with current treatments.

As requested in the draft guidance, Novartis have conducted the additional analyses outlined by the Committee:

- The company base case has been updated, using the company submission (CS) base case after correction of errors based on the external assessment group (EAG) report as a starting point (1), then by applying the preferred assumptions of the committee aligned with adjustments made by the EAG (2, 3, 4), and finally by applying the changes requested by the committee as part of the DGD (5, 6, 7):

| Case | Assumptions |
|---|---|
| (1) | CS base case after correction of errors |
| (2) | (1) + Ruxolitinib only different time to NST |
| (3) | (2) + Utility cGvHD ≤4 cycles equal to failure-free ≤4 cycles |
| (4) EAG base case | (3) + Disutility AE multiplicative |
| (5) | (4) + 1st line BAT distribution after ruxolitinib for aGvHD |
| (6) | (5) + 35% of the patients incurring wastage of ruxolitinib |
| (7) Company new base case | (6) + Disutility from non-crossover BAT patients for cGvHD, NST |

NICE National Institute for Health and Care Excellence

**Ruxolitinib for treating acute graft versus host disease refractory to corticosteroids in people aged 12 and over (review of TA839) [ID6377]**

**Draft guidance comments form**

**Consultation on the draft guidance document – deadline for comments** 5pm on Friday 10 January 2025. Please submit via NICE Docs.

Abbreviations: AE, adverse event; aGvHD, acute graft-versus-host-disease; BAT, best available therapy; cGvHD, chronic graft-versus-host-disease; CS, company submission; EAG, external assessment Group; NST, new systemic therapy.

- In addition to the updated base-case, new scenarios 1) varying the utility value for the 'chronic GvHD (cGvHD) – new systemic therapy (NST) health state and 2) applying wastage of ruxolitinib to all patients have been run, respectively, using the company new base case (Case 7).

Please see Appendix A for updated and additional results.

| Comment number | Comments<br><br>Insert each comment in a new row.<br>Do not paste other tables into this table, because your comments could get lost – type directly into this table. |
|---|---|
| 1 | **Incorporation of the committees preferred assumptions from the EAG base case**<br><br>In accordance with the committee's preferred assumptions given in the draft guidance, the following assumptions from the EAG base case have incorporated into the company base case:<br>• Extrapolating survival by assuming treatment benefit of ruxolitinib for time to new systemic treatment only<br>• Lowering the utility value for the 'cGvHD – failure-free (FF), first 4 cycles' health state<br>• Applying adverse event disutilities so that they are multiplicative.<br><br>Including these assumptions (Case 4) reduces the CS base case (Case 1) ICER (after correction of errors) from £22,703 to £17,849. The incremental impact of each change is presented in Appendix A. |
| 2 | **Distribution of therapies at third line (3L) in the ruxolitinib arm may not accurately reflect UK clinical practice**<br><br>In the company submission, the distribution of therapies at 3L (NST) in both arms included in the economic model was taken from the combined ruxolitinib and best available therapy (BAT) arms of the REACH2 trial (Table 38, page 120 of the company submission, and below).<br>**Table 38 (company submission): Distribution of BAT therapies – aGvHD NST** |

Please return to: **NICE DOCS**

**Ruxolitinib for treating acute graft versus host disease refractory to corticosteroids in people aged 12 and over (review of TA839) [ID6377]**

**Draft guidance comments form**

**Consultation on the draft guidance document – deadline for comments** 5pm on Friday 10 January 2025. Please submit via NICE Docs.

| Drug | Proportion of patients – aGvHD NST |
|---|---|
| Anti-thymocyte globulin | 10% |
| Extracorporeal photopheresis | 16% |
| Mesenchymal stromal cells | 11% |
| Low-dose methotrexate | 1% |
| Mycophenolate mofetil | 21% |
| Everolimus | 1% |
| Sirolimus | 2% |
| Etanercept | 19% |
| Infliximab | 7% |

Abbreviations: aGvHD, acute graft-versus-host-disease; BAT, best available therapy; NST, new systemic therapy.

The committee highlighted that patients who received ruxolitinib as second line (2L; model entry) aGvHD treatment in the model may be more likely to receive ECP at 3L (NST) than those in the BAT arm. To address this issue, Novartis consulted with 2 UK clinical experts who advised that it is clinically plausible to assume that in patients who receive ruxolitinib at 2L (model entry), the same distribution of BAT therapies would be applied at 3L (NST) as at 2L for aGvHD patients who are not treated with ruxolitinib (4). Thus, different treatment distributions are applied in the aGvHD – NST health state for ruxolitinib and BAT.

For patients entering the NST state in the ruxolitinib arm of the model, the proportion of patients receiving each BAT therapy is equal to the proportions in the BAT arm at model baseline. This means that the proportion of ruxolitinib patients receiving ECP at 3L (NST) increases to 45% compared to 16% for BAT. The proportion of patients receiving each treatment at 3L (NST) is presented in Table 1.

**Table 1: 3L therapies used in the aGvHD NST state in the economic analysis**

| Therapy | Proportion in the ruxolitinib arm | Proportion in the BAT arm |
|---|---|---|
| ATG | 0% | 10% |
| ECP | 45% | 16% |
| Etanercept | 15% | 19% |
| Everolimus | 0% | 1% |
| Infliximab | 15% | 7% |
| Low-dose methotrexate | 0% | 1% |
| MMF | 17% | 21% |
| MSC | 5% | 11% |
| Sirolimus | 1% | 2% |

Please return to: **NICE DOCS**

**Ruxolitinib for treating acute graft versus host disease refractory to corticosteroids in people aged 12 and over (review of TA839) [ID6377]**

**Draft guidance comments form**

**Consultation on the draft guidance document – deadline for comments** 5pm on Friday 10 January 2025. Please submit via NICE Docs.

| | |
|---|---|
| | <table><tr><td>No treatment</td><td>3%</td><td>0%</td></tr></table><br>Abbreviations: 3L, third line; ATG, anti-thymocyte globulin; BAT, best available therapy; ECP, extracorporeal photopheresis; MMF, mycophenolate mofetil; MSC, mesenchymal stromal cells.<br><br>These changes have been incorporated into the EAG base-case (Case 4) and have a minimal impact on the incremental cost-effectiveness ratio (ICER), which is increased by £1,685 (from £17,489 to £19,174) after applying the first-line (1L) BAT distribution to subsequent treatments after ruxolitinib for aGvHD patients (Case 5). The full updated base-case results can be found in Appendix A. |
| 3 | **Drug wastage**<br><br>The committee noted that, while aGvHD is treated in hospital with ruxolitinib dispensed by hospital pharmacies, there will be some people with aGvHD who are treated as outpatients and that the risk of wastage is higher among outpatients, therefore wastage should be reflected in the economic model.<br><br>A clinical expert consulted by Novartis explained that the pharmacy dispenses drugs based on patient needs and minimises wastage by dispensing one month's supply at a time (one pack). To account for this in the model, the cost of an extra half pack (28 tablets) per patient has been included, which was considered reasonable by the clinical expert, and by a second, additional expert consulted by Novartis (4). The first clinical expert estimated that 35% of patients will be treated as outpatients, and the additional cost has only been applied to these patients in the base case analysis.<br><br>Applying wastage of ruxolitinib to 35% patients (Case 6) increased the ICER by £767 (from £19,174 to £19,941) comparing to Case 5, presented in Comment 2. Full updated results are presented in Appendix A.<br><br>To aid the committee in their decision making, an additional scenario where wastage of ruxolitinib being applied to all patients has been included in Appendix A. |
| 4 | **Utility values**<br><br>The committee had concerns with the utility values used in the model, particularly the value used in the "cGvHD – NST" state, as this was comparable to those in the "aGvHD – FF" and "cGvHD – FF" states. The committee stated that this value was implausibly high, and it is likely to worsen over time.<br><br>The approach to utility analysis was discussed with a UK clinical expert who confirmed that the utility values used in the economic model are clinically plausible from their perspective. The clinical expert explained that aGvHD and cGvHD are two biologically different diseases, and it is inappropriate to directly compare utility values between them (4).<br><br>The expert explained that patients with aGvHD are often inpatients, still recovering from their transplant and with a very low QoL, high fatigue scores and often facing a life-threatening situation, meaning that if they require a new systemic therapy (i.e. 3L |

**Ruxolitinib for treating acute graft versus host disease refractory to corticosteroids in people aged 12 and over (review of TA839) [ID6377]**

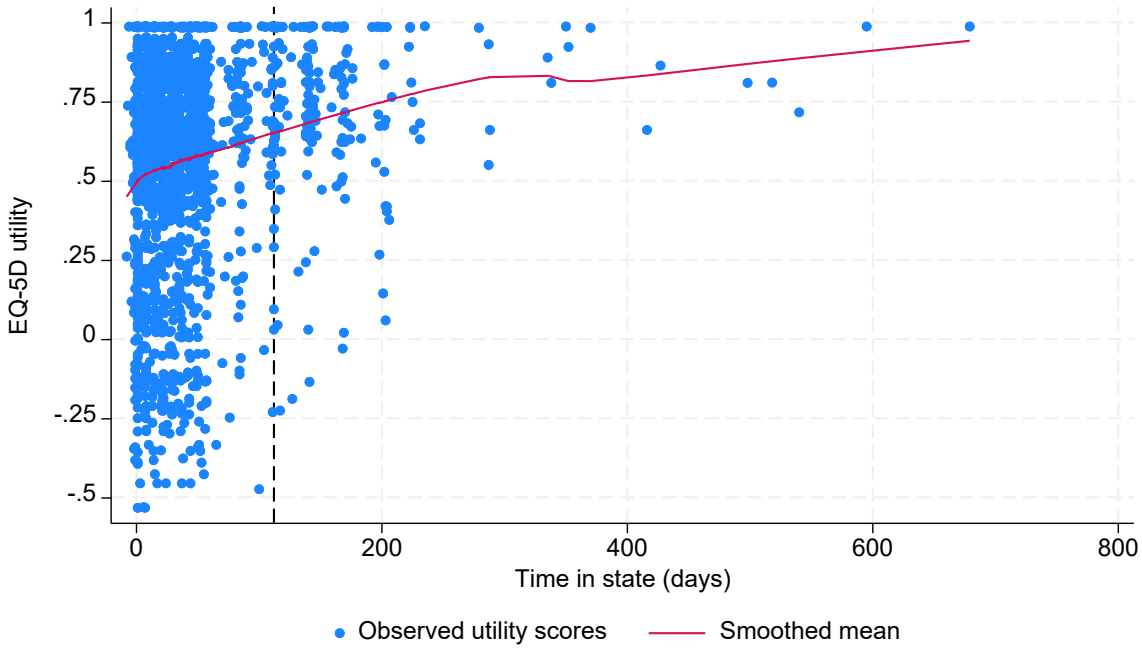
**Draft guidance comments form**

**Consultation on the draft guidance document – deadline for comments** 5pm on Friday 10 January 2025. Please submit via NICE Docs.

treatment), they can deteriorate quite quickly and thus the "acute – NST" value shows a significant drop relative to the "acute – FF" utility value. The clinical expert explained that in the chronic setting, the drivers of QoL are not the same; patients are typically ambulatory and outpatients, so the main concern is managing their symptoms (such as the psychological impact of cGvHD) as opposed to keeping them alive. This is why chronic patients will not experience a utility value that is much lower from the "chronic – FF" health state. Therefore, the expert concluded the utility values used (derived from the REACH2 and REACH3 trials) are clinically plausible.

The expert talked about the kinetics of change of therapy in the acute setting and the chronic setting being very different. This is reflected in the REACH2 trials and subsequently in the economic model. In REACH2, patients that remain failure-free experience an improvement in QoL over time (Figure 1). This is captured in the model through an improved utility value after the first 4 cycles (represented by the dashed line in Figure 1), though patients may continue to experience improvements over time.

**Figure 1: Utility values over time, aGvHD – FF**




Dashed line indicates end of Cycle 4.
Abbreviations: aGvHD, acute graft-versus-host-disease; FF, failure-free.

Utility values for the cGvHD state exhibit a different behaviour, as in the FF state (Figure 2) there is an increase from baseline in the first 6 months, after which utility values are broadly stable. In the NST health states (Figure 3), utility values for cGvHD initially decrease before increasing again and stabilising. This was also discussed with the clinical expert, who also stated that they did not expect any significant improvement over time, unlike in aGvHD.

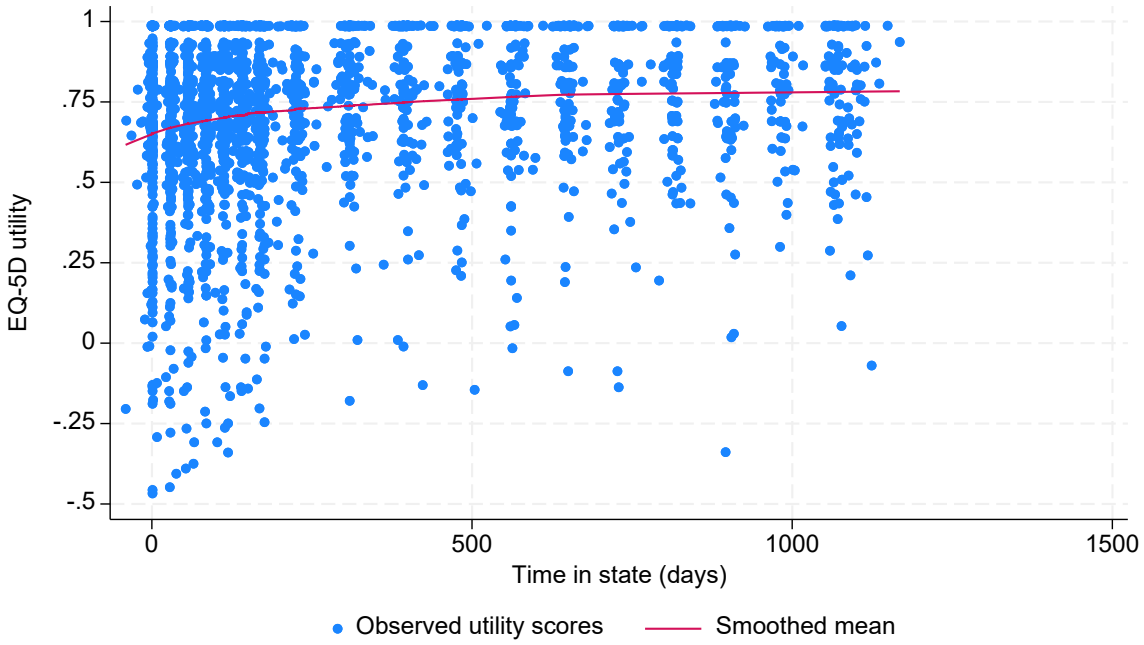
NICE National Institute for Health and Care Excellence

**Ruxolitinib for treating acute graft versus host disease refractory to corticosteroids in people aged 12 and over (review of TA839) [ID6377]**

**Draft guidance comments form**

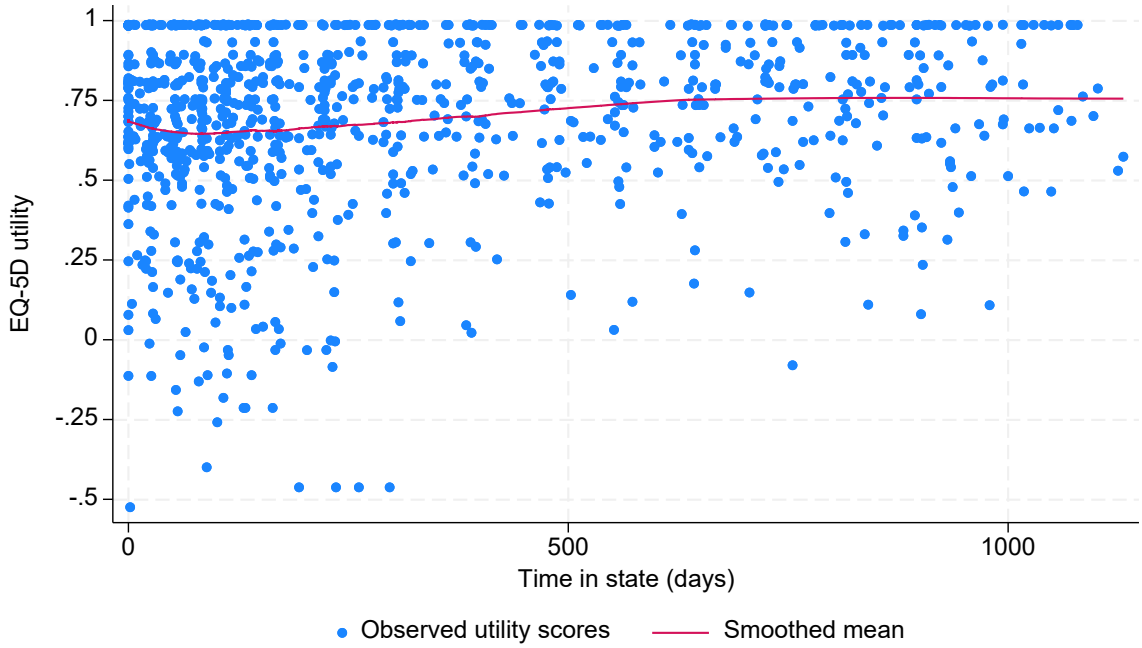
**Consultation on the draft guidance document – deadline for comments** 5pm on Friday 10 January 2025. Please submit via NICE Docs.

**Figure 2: Utility values over time, cGvHD – FF**




Abbreviations: cGvHD, chronic graft-versus-host-disease; FF, failure-free.

**Figure 3: Utility values over time, cGvHD – NST**




Abbreviations: cGvHD, chronic graft-versus-host-disease; NST, new systemic therapy.

There are little published data on utility values for SR-cGvHD, however Lachance et al, 2021 was identified in TA949. This provides EQ-5D-5L utility values from cross-sectional

Please return to: **NICE DOCS**

**Ruxolitinib for treating acute graft versus host disease refractory to corticosteroids in people aged 12 and over (review of TA839) [ID6377]**

**Draft guidance comments form**

**Consultation on the draft guidance document – deadline for comments** 5pm on Friday 10 January 2025. Please submit via NICE Docs.

| | |
|---|---|
| | survey of patients with cGvHD, though the tariff applied is unclear. This provided a mean utility value of 0.69 for patients with SR-cGvHD (5). This is comparable to the observed utility values for cGvHD FF (0.722) in pooled REACH2 and REACH3 patients, and with the utility value estimated from the regression model of 0.689 used in the CS base-case analysis (Case 1).<br><br>In the CS base case (Case 1), the utility value for the "cGvHD – NST" state is 0.673, a disutility of –0.016 compared to "cGvHD – FF". The committee stated that lower utility values are expected in the "cGvHD – NST" state as patients are expected to perform worse if they require further treatment. The utility values used in the model are based on all observed data from REACH3, however this will include a number of patients in the NST state who have crossed over from BAT to ruxolitinib. The clinical expert advised that it may be useful to look at the utility values for patients in the BAT arm who did not crossover to ruxolitinib. The mean utility for these patients was 0.706 in the "cGvHD – FF" health state, falling to 0.645 in the "cGvHD – NST state", a disutility of –0.061. This value is expected to be more reflective of the change in utility for cGvHD patients that fail treatment, when switching to ruxolitinib is not an option.<br><br>This disutility has been applied in the company new base case (Case 7) to calculate the utility for "cGvHD – NST", and the remaining values are unchanged. The impact of this change was minimal, increasing the ICER by £377 (from £19,941 to £20,318) comparing to Case 6, presented in Comment 3.<br><br>To aid the committee in their decision making, the following additional scenarios have been included in Appendix A:<br>1. Disutility taken from the regression model used in the original company base case (–0.016)<br>2. Disutility taken from the observed difference in utility for cGvHD – FF and cGvHD – NST (–0.033)<br>3. Using the preferred utility value for the NST state in TA949 (0.608).<br><br>The impact of these scenarios is minimal, with scenarios 1 and 2 leading to a small decrease in the ICER and scenario 3 leading to an increase in the ICER. The full company new base-case results and scenario analyses can be found in Appendix A. |
| 5 | **Textual clarifications, typographical errors and factual inaccuracies**<br>Novartis kindly request for the following typographical errors and factual inaccuracies in the draft guidance to be corrected:<br>• Section 3.6, page 9: "The committee noted that 38% of people in the standard-care arm switched to ruxolitinib". This should be **37%,** as per Section B.3.3.2.1, page 92 of the CS<br>• Section 3.6, pages 9-10: "The trial allowed people in the standard-care arm to switch to ruxolitinib at or after week 24" and "The committee noted that 38% of |

**Ruxolitinib for treating acute graft versus host disease refractory to corticosteroids in people aged 12 and over (review of TA839) [ID6377]**

**Draft guidance comments form**

**Consultation on the draft guidance document – deadline for comments** 5pm on Friday 10 January 2025. Please submit via NICE Docs.

people in the standard-care arm switched to ruxolitinib at or after week 24". As per the REACH3 clinical study report (6), patients could cross over on or after Day 1 of Cycle 7. As each cycle was 4 weeks long, this means the earliest they could switch would be **Week 25**

- Section 3.7, page 11: "The EAG noted that REACH2 showed an increase in average utility of people in REACH2 in failure-free survival after 4 weeks…". This should be "after 4 **cycles**", as per the model
- Section 3.10, page 15: please update the values in Table 2 of the draft guidance with those of Table 4.16 of the EAG report

| Treatment | Proportion of people (%) |
|---|---|
| Mycophenolate mofetil | **23** |
| ECP | **17** |
| Etanercept | **21** |
| Mesenchymal stromal cells | **12** |
| Antithymocyte globulin | **11** |
| Infliximab | 7 |
| Sirolimus | 2 |
| Low-dose methotrexate | 1 |
| Everolimus | 1 |
| **No treatment** | **3** |

**Checklist for submitting comments**

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

**Ruxolitinib for treating acute graft versus host disease refractory to corticosteroids in people aged 12 and over (review of TA839) [ID6377]**

**Draft guidance comments form**

**Consultation on the draft guidance document – deadline for comments** 5pm on Friday 10 January 2025. Please submit via NICE Docs.

- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

**Note:** We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

## References


1. National Institute for Health and Care Excellence (NICE). Draft guidance consultation. Ruxolitinib for treating acute graft versus host disease that responds inadequately to corticosteroids in people 12 years and over. 2024.
2. Novartis. Data on file. Validation call with clinical expert from Scotland - August 2024. CONFIDENTIAL. 2024.
3. Novartis. Data on file. UK Clinicians interviews February–March 2024. Consolidated report. CONFIDENTIAL. 2024.
4. Novartis. Data on file. Calls with clinical experts to support FDG response – combined report. CONFIDENTIAL. 2024.
5. Lachance S, Hamad N, De Courcy J, Gibson G, Zuurman M, M M. Impact of Chronic Gvhd Severity And Steroid Response on The Quality of Life In Patients Following Allogeneic Stem Cell Transplantation: Findings From A Real-World Study. Bone marrow transplantation. 2021;56:83-4.
6. Novartis. REACH3 Primary Analysis Clinical Study Report. CONFIDENTIAL. 2020.


Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

**Ruxolitinib for treating acute graft versus host disease refractory to corticosteroids in people aged 12 and over (review of TA839) [ID6377]**

**Draft guidance comments form**

**Consultation on the draft guidance document – deadline for comments** 5pm on Friday 10 January 2025. Please submit via NICE Docs.

# Appendix A: Additional analyses requested by the committee

## Updated economic analyses

***Base case***

Following the draft guidance, the step-by-step changes have been made to derive the new company base case, using the CS base case after correction of errors based on the EAG report as starting point.

The following preferred assumptions of the committee aligned with adjustments made by the EAG were applied to the CS base case after correction of errors:

- Extrapolating survival by assuming treatment benefit of ruxolitinib for time to new systemic treatment only
- Lowering the utility value for the 'cGvHD – FF, first 4 cycles' health state
- Applying adverse event disutilities so that they are multiplicative.

In addition, the following changes requested by the committee were updated in the economic analysis based on the EAG base case:

- Different distribution of subsequent treatments for aGvHD depending on whether previous treatment was ruxolitinib or standard of care
- The expected cost of wastage of ruxolitinib
- Changing the utility value for the 'cGvHD – NST' health state.

Based on the EAG base case (Case 4), 1L BAT distribution was applied to subsequent treatments after ruxolitinib for aGvHD patients (Case 5). In addition, the cost of an additional half pack of ruxolitinib has been added to 35% of the patients in the ruxolitinib arm to capture the wastage of ruxolitinib among outpatients (Case 6). Moreover, the difference in utility values modelled between the cGvHD – FF and cGvHD – NST health states observed in BAT patients who did not crossover to ruxolitinib was used in the company's new base case (–0.061) (Case 7).

The cumulative impact of each assumption is presented in Table 2. The ICER increased by £1,685 after applying the 1L BAT distribution to subsequent treatments after ruxolitinib for aGvHD patients. Inclusion of wastage increased the ICER by £767. The impact of updated utility value had little impact on the ICER, which increased by £377.

NICE National Institute for Health and Care Excellence

# Ruxolitinib for treating acute graft versus host disease refractory to corticosteroids in people aged 12 and over (review of TA839) [ID6377]

## Draft guidance comments form

**Consultation on the draft guidance document – deadline for comments** 5pm on Friday 10 January 2025. Please submit via NICE Docs.

**Table 2: Base-case results (deterministic), with [redacted] price**

| Technologies | Total costs (£) | Total QALYs | Incremental. costs (£) | Incremental QALYs | ICER (£/QALY) | ICER with severity modifier (£/QALY) |
|---|---|---|---|---|---|---|
| **CS base case after correction of errors** | | | | | | |
| BAT | £80,521 | 1.32 | – | – | – | – |
| Ruxolitinib ([redacted] price) | [redacted] | [redacted] | [redacted] | [redacted] | £27,243 | £22,703 |
| **+ Ruxolitinib only different time to NST** | | | | | | |
| BAT | £83,878 | 1.39 | – | – | – | – |
| Ruxolitinib ([redacted] price) | [redacted] | [redacted] | [redacted] | [redacted] | £21,021 | £17,517 |
| **+ Utility cGvHD ≤4 cycles equal to failure-free ≤4 cycles** | | | | | | |
| BAT | £83,878 | 1.39 | – | – | – | – |
| Ruxolitinib ([redacted] price) | [redacted] | [redacted] | [redacted] | [redacted] | £21,010 | £17,508 |
| **+ Disutility AE multiplicative (EAG base case)** | | | | | | |
| BAT | £83,878 | 1.39 | – | – | – | – |
| Ruxolitinib ([redacted] price) | [redacted] | [redacted] | [redacted] | [redacted] | £20,987 | £17,489 |
| **+ 1st line BAT distribution after ruxolitinib for a GvHD** | | | | | | |
| BAT | £83,878 | 1.39 | – | – | – | – |
| Ruxolitinib ([redacted] price) | [redacted] | [redacted] | [redacted] | [redacted] | £23,009 | £19,174 |
| **+ 35% of the patients incurring wastage of ruxolitinib** | | | | | | |
| BAT | £83,878 | 1.39 | – | – | – | – |
| Ruxolitinib ([redacted] price) | [redacted] | [redacted] | [redacted] | [redacted] | £23,929 | £19,941 |
| **+ Disutility from non-crossover BAT patients for cGvHD, NST** | | | | | | |
| BAT | £83,878 | 1.35 | – | – | – | – |
| Ruxolitinib ([redacted] price) | [redacted] | [redacted] | [redacted] | [redacted] | £24,382 | £20,318 |

Abbreviations: AE, adverse event; aGvHD, acute graft-versus-host-disease; BAT, best available therapy; [redacted]; cGvHD, chronic graft-versus-host-disease; CS, company submission; ICER, incremental cost-effectiveness ratio; NST, new systemic treatment; QALY, quality-adjusted life year.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

**Ruxolitinib for treating acute graft versus host disease refractory to corticosteroids in people aged 12 and over (review of TA839) [ID6377]**

**Draft guidance comments form**

**Consultation on the draft guidance document – deadline for comments** 5pm on Friday 10 January 2025. Please submit via NICE Docs.

**New scenarios**

Table 3 summarises new scenarios which vary the utility value for the 'cGvHD – NST' health state and the percentage of patients incurring wastage of ruxolitinib, with the results of the scenario analyses presented in Table 4. All scenarios have been run based on the revised base case results in Table 2, using the [redacted] price for ruxolitinib and list prices for BAT.

**Table 3: New scenario analyses**

| Scenario | Details | Disutility vs cGvHD – FF | cGvHD – NST utility |
|---|---|---|---|
| Observed difference in non-crossover BAT patients | Observed difference in utility between cGvHD – FF and cGvHD – NST in BAT patients that did not crossover to ruxolitinib. This is the value used in the base case. | –0.061 | 0.628 |
| Disutility per the regression model | Applies the difference in utility between cGvHD – FF and cGvHD – NST implied by the regression model used in the base case. This is the company base case at submission. | –0.016 | 0.673 |
| Disutility in the observed data | Use the difference in the mean utility values between cGvHD – FF and cGvHD – NST health state when including patients that crossed over to ruxolitinib | –0.033 | 0.656 |
| EAG preference from TA949 | Use the EAG preferred value from TA949 | –0.081 | 0.608 |
| All patients incurring wastage of ruxolitinib | 100% of the patients incur wastage of ruxolitinib | – | – |

Abbreviations: BAT, best available therapy; cGvHD, chronic graft-versus-host-disease; EAG, external assessment group; FF, failure-free; ICER, incremental cost-effectiveness ratio; NST, new systemic therapy; TA, technology appraisal.

**Ruxolitinib for treating acute graft versus host disease refractory to corticosteroids in people aged 12 and over (review of TA839) [ID6377]**

**Draft guidance comments form**

**Consultation on the draft guidance document – deadline for comments** 5pm on Friday 10 January 2025. Please submit via NICE Docs.

**Table 4: Scenario analyses results, with [redacted] price**

| Scenario | Incremental costs | Incremental QALYs | ICER | ICER with severity modifier |
|---|---|---|---|---|
| Observed difference in non-crossover BAT patients (base case) | [redacted] | [redacted] | £24,382 | £20,318 |
| Disutility per regression models | [redacted] | [redacted] | £23,929 | £19,941 |
| Disutility in the observed data | [redacted] | [redacted] | £24,097 | £20,081 |
| EAG preference from TA949 | [redacted] | [redacted] | £24,591 | £20,492 |
| All patients incurring wastage of ruxolitinib | [redacted] | [redacted] | £26,122 | £21,768 |

Abbreviations: BAT, best available therapy; [redacted]; cGvHD, chronic graft-versus-host-disease; EAG, external assessment group; FF, failure-free; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TA, technology appraisal.

**Probabilistic sensitivity analysis**

Table 5 presents the results of probabilistic sensitivity analysis (PSA) based on the company new base case (Case 7) (5,000 Monte Carlo simulations were recorded). The PSA results are congruent with the deterministic results, and ruxolitinib remains cost-effective (£19,897) at the [redacted] price, and the comparator list prices. Figure 4 presents the cost-effectiveness plane (CEP). The cost-effectiveness acceptability curve (CEAC) (Figure 5) shows that ruxolitinib was dominant in [redacted]% of simulations and was cost-effective in [redacted]% and [redacted]% of simulations at a willingness-to-pay (WTP) threshold of £20,000 per QALY without and with the severity modifier, respectively, and [redacted]% and [redacted]% of simulations at a WTP threshold of £30,000 per QALY without and with the severity modifier, respectively.

**Table 5: PSA results based on the company new base case (Case 7) (ruxolitinib [redacted] price)**

| Technologies | Total costs (£) | Total QALYs | Incremental. costs (£) | Incremental QALYs | ICER (£/QALY) | ICER with severity modifier (£/QALY) |
|---|---|---|---|---|---|---|
| BAT | £82,845 | 1.33 | – | – | – | – |
| Ruxolitinib ([redacted] price) | [redacted] | [redacted] | [redacted] | [redacted] | £23,876 | £19,897 |

Analysis uses [redacted] price for ruxolitinib and list price for comparators.

Abbreviations: BAT, best available therapy; [redacted]; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

NICE National Institute for Health and Care Excellence

**Ruxolitinib for treating acute graft versus host disease refractory to corticosteroids in people aged 12 and over (review of TA839) [ID6377]**

**Draft guidance comments form**

**Consultation on the draft guidance document – deadline for comments** 5pm on Friday 10 January 2025. Please submit via NICE Docs.

**Figure 4: Cost-effectiveness plane (ruxolitinib [redacted] price, with modifier)**

Abbreviations: BAT, best available therapy; [redacted]; QALY, quality-adjusted life year.

**Figure 5: Cost-effectiveness acceptability curve (ruxolitinib [redacted] price, with and without modifier)**

Abbreviations: BAT, best available therapy; [redacted]; QALY, quality-adjusted life year.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

**Ruxolitinib for treating acute graft versus host disease refractory to corticosteroids in people aged 12 and over (review of TA839) [ID6377]**

**Draft guidance comments form**

**Consultation on the draft guidance document – deadline for comments** 5pm on Friday 10 January 2025. Please submit via NICE Docs.

| | |
|---|---|
| | Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.<br><br>The Appraisal Committee is interested in receiving comments on the following:<br>• has all of the relevant evidence been taken into account?<br>• are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?<br>• are the provisional recommendations sound and a suitable basis for guidance to the NHS?<br><br>NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:<br>• could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology;<br>• could have any adverse impact on people with a particular disability or disabilities.<br><br>Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.** |
| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | Anthony Nolan |

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

**Ruxolitinib for treating acute graft versus host disease refractory to corticosteroids in people aged 12 and over (review of TA839) [ID6377]**

**Draft guidance comments form**

**Consultation on the draft guidance document – deadline for comments** 5pm on Friday 10 January 2025. Please submit via NICE Docs.

| | |
|---|---|
| **Disclosure**<br>Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.]<br>Please state:<br>• the name of the company<br>• the amount<br>• the purpose of funding including whether it related to a product mentioned in the stakeholder list<br>• whether it is ongoing or has ceased. | **Anthony Nolan**<br>**Sanofi:** We received a grant of **£20,000** to support the development of a report highlighting the psychological impact of stem cell transplant and CAR-T on patients and families. Separately we have received **£4,200** from Sanofi to provide input into the design of a patient survey on the topic of GvHD.<br>**Pfizer:** We received **£300** to attend an advisory board to develop principles of care to inform a Blood Cancer Patient Charter.<br>**Therakos:** We have received funding for 2 x staff roles (over two years) of £100k over 2 years: 01/09/21 - 31/08/23. Therakos employees have also donated sponsorship towards the London Parks Half marathon of £3,150 and entrance fees totalling £225. |
| Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | Not applicable. |
| **Name of commentator person completing form:** | [redacted] |

| **Comment number** | **Comments**<br>Insert each comment in a new row.<br>Do not paste other tables into this table, because your comments could get lost – type directly into this table. |
|---|---|
| Example 1 | We are concerned that this recommendation may imply that …….. |
| 1 | Anthony Nolan is concerned that this draft no recommendation will exacerbate existing inequalities for those living with acute GvHD which have been extensively outlined in the committee papers, such as those with limited means or physical ability to travel to specialist treatment centres. In the |

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

**Ruxolitinib for treating acute graft versus host disease refractory to corticosteroids in people aged 12 and over (review of TA839) [ID6377]**

**Draft guidance comments form**

**Consultation on the draft guidance document – deadline for comments** 5pm on Friday 10 January 2025. Please submit via NICE Docs.

| | |
|---|---|
| | draft decision, the committee has concluded that equity concerns we and others raised "were not relevant equality considerations that could be addressed in its decision making in a technology appraisal." We are of the opinion that NICE's process for considering equity concerns is too restrictive and it is not clear to us why equity concerns cannot be factored into the decision. |
| 2 | When considering utility values, the committee concluded that "the utility value for the 'chronic GvHD – new systemic treatment' was implausibly high and would probably worsen over time". We would like to note that acute and chronic GvHD have different impacts on patients and in many cases people with chronic GvHD are managed out of hospital and this has a positive impact on their quality of life. Many chronic GvHD patients are able to manage their chronic GvHD with treatment, and some have even gone back into full-time employment. |
| 3 | Overall, we feel that the draft recommendation does not take into full consideration the potential equality and quality of life benefits of ruxolitinib over existing treatments for acute GVHD. |

Insert extra rows as needed

**Checklist for submitting comments**

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

**Note:** We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

# Ruxolitinib for treating acute graft versus host disease refractory to corticosteroids in people aged 12 and over (review of TA839) [ID6377]

## Draft guidance comments form

**Consultation on the draft guidance document – deadline for comments** 5pm on Friday 10 January 2025. Please submit via NICE Docs.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

**Ruxolitinib for treating acute graft versus host disease refractory to corticosteroids in people aged 12 and over (review of TA839) [ID6377]**

**Draft guidance comments form**

**Consultation on the draft guidance document – deadline for comments** 5pm on Friday 10 January 2025. Please submit via NICE Docs.

| | |
|---|---|
| | Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.<br><br>The Appraisal Committee is interested in receiving comments on the following:<br>• has all of the relevant evidence been taken into account?<br>• are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?<br>• are the provisional recommendations sound and a suitable basis for guidance to the NHS?<br><br>NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:<br>• could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology;<br>• could have any adverse impact on people with a particular disability or disabilities.<br><br>Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.** |
| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | NHS England Specialised Commissioning |

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

**Ruxolitinib for treating acute graft versus host disease refractory to corticosteroids in people aged 12 and over (review of TA839) [ID6377]**

**Draft guidance comments form**

**Consultation on the draft guidance document – deadline for comments** 5pm on Friday 10 January 2025. Please submit via NICE Docs.

| | |
|---|---|
| **Disclosure**<br>Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.]<br>Please state:<br>• the name of the company<br>• the amount<br>• the purpose of funding including whether it related to a product mentioned in the stakeholder list<br>• whether it is ongoing or has ceased. | None |
| Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | None |
| **Name of commentator person completing form:** | [redacted] |

| **Comment number** | **Comments**<br>Insert each comment in a new row.<br>Do not paste other tables into this table, because your comments could get lost – type directly into this table. |
|---|---|
| Example 1 | We are concerned that this recommendation may imply that …….. |
| 1 | The NHSE Blood and Marrow Transplantation (BMT) Clinical Reference Group (CRG) have several concerns regarding this negative recommendation. |

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

**Ruxolitinib for treating acute graft versus host disease refractory to corticosteroids in people aged 12 and over (review of TA839) [ID6377]**

**Draft guidance comments form**

**Consultation on the draft guidance document – deadline for comments** 5pm on Friday 10 January 2025. Please submit via NICE Docs.

| | |
|---|---|
| | The CRG are concerned that the inequalities have not been fully taken into account when reaching this decision. Some patients can struggle to receive extracorporeal photopheresis (ECP) treatment due to work or caring commitments, lack of means to arrange transport to the hospital or lack of physical ability to make the journey to the hospital. Ruxolitinib would offer a treatment option for all patients as it is an oral tablet. |
| 2 | It is noted that the "utility value for the chronic GVHD -new systemic treatment" was very high and could get worse with time. The CRG would like to advise the committee that the vast majority of patients with chronic GVHD are out-patients and can manage their symptoms reasonably well. Some of this group have also returned to work or caring responsibilities. |
| 3 | |
| 4 | |
| 5 | |
| 6 | |

Insert extra rows as needed

**Checklist for submitting comments**

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

# Ruxolitinib for treating acute graft versus host disease refractory to corticosteroids in people aged 12 and over (review of TA839) [ID6377]

## Draft guidance comments form

**Consultation on the draft guidance document – deadline for comments** 5pm on Friday 10 January 2025. Please submit via NICE Docs.

**Note:** We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

**Ruxolitinib for treating acute graft versus host disease refractory to corticosteroids in people aged 12 and over (review of TA839) [ID6377]**

**Draft guidance comments form**

**Consultation on the draft guidance document – deadline for comments** 5pm on Friday 10 January 2025. Please submit via NICE Docs.

| | |
|---|---|
| | Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.<br><br>The Appraisal Committee is interested in receiving comments on the following:<br>• has all of the relevant evidence been taken into account?<br>• are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?<br>• are the provisional recommendations sound and a suitable basis for guidance to the NHS?<br><br>NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:<br>• could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology;<br>• could have any adverse impact on people with a particular disability or disabilities.<br><br>Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.** |
| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | Therakos UK Ltd |

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

**Ruxolitinib for treating acute graft versus host disease refractory to corticosteroids in people aged 12 and over (review of TA839) [ID6377]**

**Draft guidance comments form**

**Consultation on the draft guidance document – deadline for comments** 5pm on Friday 10 January 2025. Please submit via NICE Docs.

| | |
|---|---|
| **Disclosure**<br>Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.]<br>Please state:<br>• the name of the company<br>• the amount<br>• the purpose of funding including whether it related to a product mentioned in the stakeholder list<br>• whether it is ongoing or has ceased. | None |
| Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | None |
| **Name of commentator person completing form:** | [redacted] |

| **Comment number** | **Comments**<br><br>Insert each comment in a new row.<br>Do not paste other tables into this table, because your comments could get lost – type directly into this table. |
|---|---|
| Example 1 | We are concerned that this recommendation may imply that …….. |
| 1 | Section 3.21, page 22: Draft Guidance. Therakos UK agrees with the draft guidance. |
| 2 | Source: Section 3.2, page 6: Draft Guidance. '*The patient experts explained that some people must commit significant time and money to travel for* |

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

**Ruxolitinib for treating acute graft versus host disease refractory to corticosteroids in people aged 12 and over (review of TA839) [ID6377]**

**Draft guidance comments form**

**Consultation on the draft guidance document – deadline for comments** 5pm on Friday 10 January 2025. Please submit via NICE Docs.

| | |
|---|---|
| | *treatment, require invasive venous access, and often have long hospital stays'* Long hospital stays are often the result of the disease severity and complications and is not associated with the administration of extracorporeal photopheresis (ECP). |
| 3 | Source, Section: 3.2, page 5 Draft Guidance. '*ECP is available at a few therapeutic apheresis services and a limited number of hospital trusts. '*& Source: page 28, Consolidated Document B, '*ECP Available in 5 Therapeutic Apheresis centres across England and Wales and a limited number of hospital trusts provide ECP services independently'.* There are 29 NHS sites where ECP is available for patients currently. This is subject to change as we adapt to the requirements of the current sites and requests for new sites. |
| 4 | |
| 5 | |
| 6 | |

Insert extra rows as needed

**Checklist for submitting comments**

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

**Note:** We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

**Ruxolitinib for treating acute graft versus host disease refractory to corticosteroids in people aged 12 and over (review of TA839) [ID6377]**

**Draft guidance comments form**

**Consultation on the draft guidance document – deadline for comments** 5pm on Friday 10 January 2025. Please submit via NICE Docs.

comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

**Ruxolitinib for treating acute graft versus host disease refractory to corticosteroids in people aged 12 and over (review of TA839) [ID6377]**

**Draft guidance comments form**

**Consultation on the draft guidance document – deadline for comments** 5pm on Friday 10 January 2025. Please submit via NICE Docs.

| | |
|---|---|
| | Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.<br><br>The Appraisal Committee is interested in receiving comments on the following:<br>• has all of the relevant evidence been taken into account?<br>• are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?<br>• are the provisional recommendations sound and a suitable basis for guidance to the NHS?<br><br>NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:<br>• could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology;<br>• could have any adverse impact on people with a particular disability or disabilities.<br><br>Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.** |
| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | Dr Donal McLornan<br><br>Consultant in Haematology and Stem Cell Transplantation |

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

**Ruxolitinib for treating acute graft versus host disease refractory to corticosteroids in people aged 12 and over (review of TA839) [ID6377]**

**Draft guidance comments form**

**Consultation on the draft guidance document – deadline for comments** 5pm on Friday 10 January 2025. Please submit via NICE Docs.

| | |
|---|---|
| **Disclosure**<br>Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.]<br>Please state:<br>• the name of the company<br>• the amount<br>• the purpose of funding including whether it related to a product mentioned in the stakeholder list<br>• whether it is ongoing or has ceased. | As per submitted COI |
| Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | Nil |
| **Name of commentator person completing form:** | Donal McLornan |

| **Comment number** | **Comments**<br><br>Insert each comment in a new row.<br>Do not paste other tables into this table, because your comments could get lost – type directly into this table. |
|---|---|
| Example 1 | We are concerned that this recommendation may imply that …….. |
| 1 | Acute GVHD remains a major complication following allogeneic hematopoietic stem cell transplantation (HSCT), leading to significant morbidity and mortality in affected patients. Ruxolitinib, a selective Janus kinase (JAK) 1/2 inhibitor, has demonstrated substantial |

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

**Ruxolitinib for treating acute graft versus host disease refractory to corticosteroids in people aged 12 and over (review of TA839) [ID6377]**

**Draft guidance comments form**

**Consultation on the draft guidance document – deadline for comments** 5pm on Friday 10 January 2025. Please submit via NICE Docs.

| | |
|---|---|
| | clinical benefit in the management of this life-threatening condition, offering an important therapeutic option for patients who have limited treatment choices. |
| 2 | We remain significantly disadvantaged in the UK compared to many countries because we do not have routine access to this drug and this places significant burden on both allo-HCT recipients and their clinical teams as you will be aware. Steroid-refractory aGVHD remains a serious challenge in clinical practice, with limited effective therapies available. The risk of progression to severe GVHD, organ damage, and fatal outcomes increases as patients fail first-line steroid therapy. Refractory aGVHD has historically been associated with high mortality rates, and new therapeutic options are urgently needed |
| 3 | The availability of ruxolitinib as a treatment option allows for more individualized management, enhancing the overall treatment landscape for aGVHD and improving patient quality of life. |
| 4 | By improving ORR, ruxolitinib could reduce the need for prolonged hospitalizations and intensive care, potentially leading to lower healthcare costs in the long run. Additionally, by improving survival and quality of life, ruxolitinib can help reduce the long-term economic burden associated with chronic GVHD, which often requires ongoing medical care and management. |
| 5 | Ruxolitinib is recommended in multiple national and international clinical guidelines for the management of steroid-refractory aGVHD, reinforcing its clinical significance and the need for its widespread availability. Its inclusion in these guidelines further validates its role as a key therapeutic option for aGVHD patients and underscores the importance of its reimbursement for broader access. Timely initiation of ruxolitinib therapy in patients with steroid-refractory GVHD is an important factor to improve outcomes in this patient population. The most recent guidelines published by the EBMT- the European authority on Stem Cell Transplantation- on GVHD management mandate the use of ruxolitinib in steroid refractory aGVHD. The barriers preventing routine access need to be removed to align with standard stem cell transplant practice. |
| 6 | I disagree with the committees assumption that the REACH2 trial design led to inherent uncertainty in its results, in the context that more patients in the standard arm were potentially switched inflating the number of treatment failures. |
| 7 | In addition, given the disparity in access to ruxolitinib in England compared to Wales and Scotland, I would stress that there is a major equality issue by not having access to this agent in England and that this should not be ignored |

Insert extra rows as needed

**Checklist for submitting comments**

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

**Ruxolitinib for treating acute graft versus host disease refractory to corticosteroids in people aged 12 and over (review of TA839) [ID6377]**

**Draft guidance comments form**

**Consultation on the draft guidance document – deadline for comments** 5pm on Friday 10 January 2025. Please submit via NICE Docs.

- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

**Note:** We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Please return to: **NICE DOCS**


in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

# Ruxolitinib for treating acute graft-versus-host disease refractory to corticosteroids in people aged 12 and over [ID6377]: EAG critique of consultation response

**Produced by** Kleijnen Systematic Reviews (KSR) Ltd., in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

**Authors**

Nigel Armstrong, Health Economics Manager, KSR Ltd, United Kingdom (UK)
Isaac Corro Ramos, Health Economics Researcher, Institute for Medical Technology Assessment (iMTA), EUR, the Netherlands (NL)
Venetia Qendri, Research Associate Health Technology Assessment (HTA), Erasmus School of Health Policy & Management (ESHPM), EUR, the NL
Annemieke van Dongen-Leunis, Assistant Professor HTA, ESHPM, EUR, the NL
Mubarak Patel, Systematic Reviewer, KSR Ltd, UK
Xiaoyu Tian, Health Economist/Systematic Reviewer, KSR Ltd, UK
Jiongyu Chen, Health Economist/Systematic Reviewer, KSR Ltd, UK
Lisa Stirk, Senior Information Specialist, KSR Ltd, UK
Maiwenn Al, Senior Lecturer HTA, ESHPM, EUR, the NL
Robert Wolff, Managing Director, KSR Ltd, UK

**Correspondence to**

Nigel Armstrong
Kleijnen Systematic Reviews Ltd
Unit 6, Escrick Business Park
Riccall Road, York
YO19 6FD, United Kingdom

**Date completed** 23 January 2025

# Introduction

This document provides the External Assessment Group's (EAG's) critique of the materials submitted to the National Institute for Health and Care Excellence (NICE) in response to the Draft Guidance Document (DGD) issued following the first technology appraisal committee meeting for ruxolitinib for treating acute graft-versus-host disease. Materials were submitted by the company plus several other stakeholders. The EAG critique focuses on the company's DGD response.

# EAG critique of company's response

## Comment 1: Incorporation of the committees preferred assumptions from the EAG base case

Based on the committee's preferred assumptions given in the draft guidance, the company has included the following assumptions from the EAG base case into the new company base case:

- Extrapolating survival by assuming treatment benefit of ruxolitinib for time to new systemic treatment only
- Lowering the utility value for the 'cGvHD – failure-free (FF), first 4 cycles' health state
- Applying adverse event disutilities so that they are multiplicative.

Including these assumptions reduces the original CS base case ICER (after correction of errors) from £22,703 to £17,489.

## Comment 2: Distribution of therapies at third line (3L) in the ruxolitinib arm may not accurately reflect UK clinical practice

In the company submission, the distribution of therapies at 3L in both arms, i.e. when patients move from the failure free state to the NST state, was taken from the pooled ruxolitinib and best available therapy (BAT) arms of the REACH2 trial (Table 38, page 120 of the company submission).

However, as the committee stated in the draft guidance (DG), it is plausible that patients who received ruxolitinib as initial treatment (second line, first line being steroid treatment) for aGvHD are more likely to receive ECP at 3L (NST) than those in the BAT arm who move to NST. After all, in the BAT arm already 45% received ECP as their initial treatment, and this may now be the treatment of choice for ruxolitinib patients moving to 3L. To address this issue, Novartis consulted with 2 UK clinical experts who advised that it is clinically plausible to assume that in patients who receive ruxolitinib at 2L (model entry), the same distribution of BAT therapies would be applied at 3L (NST) as at 2L for aGvHD patients who are not treated with ruxolitinib. Thus, different treatment distributions are applied in the aGvHD – NST health state for ruxolitinib and BAT.

Table 1 of the company's response to the DG lists these distributions of therapies for patients moving to NST from ruxolitinib (is equal to 2L for BAT) and from BAT (is equal to the 3L distribution from the CS).

Implementing this change leads to an increase in the ICER from £17,489 to £19,174, due to a small increase in the total costs for ruxolitinib.

**EAG comment:**

The EAG considers this a reasonable approach, though an alternative could have been to use the observed NST treatments separately for patients from the ruxolitinib and BAT arm, rather than using the distribution based on the pooled data on the NST received.

## Comment 3: Drug wastage

In the DG document the committee remarked that the company model assumed no wastage of ruxolitinib. According to the committee some wastage should be taken into account, as not all patients with aGvHD will be treated in a hospital and the risk of wastage is higher among outpatients

The company consulted a clinical expert, and they explained that the pharmacy dispenses drugs based on patient needs and minimises wastage by dispensing one month's supply at a time (one pack = 56 tablets). Thus, the company has now assumed that on average, a half pack (28 tablets) per patient will be wasted, and these costs have now been included in the model. This assumption was considered reasonable by the clinical expert, and by a second, additional expert consulted by the company. In addition, the first clinical expert estimated that 35% of patients will be treated as outpatients, and the additional cost has only been applied to these patients in the base case analysis.

Adding this wastage for 35% of patients increases the ICER slightly, from £19,174 to £19,941 per QALY gained. In a scenario the company explored the impact of assuming wastage in all patients, this would increase the ICER to £21,768.

**EAG comments**:

Assuming that ruxolitinib is indeed in general dispensed on a monthly basis, the assumption that on average half a month's supply may be wasted appears reasonable. Regarding the assumption that 35% of patients receives treatment on an outpatient basis, this might be validated with data from the REACH2 study, by looking at the percentage of patients being discharged from hospital whilst still receiving treatment with ruxolitinib and the percentage of patients not being hospitalised at all.

However, the scenario analysis from the company indicates that even if all patients waste half a package of ruxolitinib, the impact on the ICER is limited.

## Comment 4: Utility values

In the guidance document the committee expressed concern regarding the face validity of the utility values in the cGvHD health states. This concern was mainly about the utility for cGvHD NST, as this value is more or less similar to the utility for cGvHD Failure-free and aGvHD FF after 4 cycles. The committee considered this unlikely, as they expect that patients will experience worst quality of life with each subsequent line of treatment, and that this quality of life will worsen over time.

Based on these comments the company conculted with an UK clinical expert who confirmed that the utilities used in the model are clinically plausible, given the difference in nature between aGvHD and cGvHD. Whilst with aGvHD patients can be quite sick, where the aim of treatment is primarily to keep the patient alive, and patients can quickly deteriorate (hence the drop in utility when they move to theNST health state), patients with cGvHD are typically ambulatory and treated as outpatients, with a much smaller decrease in quality of life when they need a next treatment.

To show the difference in how QoL develops over time, the company included figure in their response with utility values over time, for the aGvHD – failure-free, cGvHD – failure-free, and cGvHD – NST

heath states. These figures show for the acute heath state a steadily rising utility over time, whereas for the chronic failure free state the utilities first slowly increase after which they become more or less constant whilst the chronic NST state shows initially a slight drop in the first few weeks followed, by first an increase and then again a more or less constant utility.

In the CS base case, a utility value of 0.673 was used for the "cGvHD – NST" state, a disutility of –0.016 compared to "cGvHD – FF". This utility value, as well as those of the other chronic states is based on all observed data from REACH3. However, that data also includes a number of patients in the NST state who have crossed over from BAT to ruxolitinib and the clinical expert advised that it may be useful to look at the utility values for patients in the BAT arm who did not crossover to ruxolitinib. The mean utility for these patients was 0.706 in the "cGvHD – FF" health state, falling to 0.645 in the "cGvHD – NST state", a disutility of –0.061. The company expects this value to be more reflective of the change in utility for cGvHD patients that fail treatment, when switching to ruxolitinib is not an option.

This disutility has been applied in the new company base case to calculate the utility for "cGvHD – NST", whilst the remaining values are unchanged. The impact of this change was minimal, increasing the ICER from £19,941 to £20,318.

Furthermore, the company explored three different scenarios for the cGvHD – NST utility:

- Applying the original disutility of -0.016
- Applying a disutility based on the observed difference in utility for cGvHD – FF (0.722) and cGvHD – NST (0.689), which is -0.033
- Using the preferred utility value for the NST state in TA949 of 0.608

For all these scenarios the impact on the ICER is very minimal.

**EAG comment:**

The EAG considers the new base case disutility a plausible value, taking into account the nature of chronic GvHD and the observed utilities in REACH3. By limiting the analysis to only patients who did not cross-over a potential source of distortion has been eliminated.

## Company's results of updated cost effectiveness model

Following the draft guidance, the step-by-step changes have been made to derive the new company base case, using the CS base case after correction of errors based on the EAG report as starting point.

The following preferred assumptions of the committee aligned with adjustments made by the EAG were applied to the CS base case after correction of errors:

- Extrapolating survival by assuming treatment benefit of ruxolitinib for time to new systemic treatment only
- Lowering the utility value for the 'cGvHD – FF, first 4 cycles' health state
- Applying adverse event disutilities so that they are multiplicative.

In addition, the company made the flowing changes based on the requests by the committee:

- Different distribution of subsequent treatments for aGvHD depending on whether previous treatment was ruxolitinib or standard of care
- The expected cost of wastage of ruxolitinib
- Changing the utility value for the 'cGvHD – NST' health state.

The EAG has checked the implementation of all the below mentioned changes into the model and did not find any issues.

Table 1 shows how each of these adjustments impact the results.

**Table 1 Base-case results (deterministic), with [redacted] price**

| Technologies | Total costs (£) | Total QALYs | Incremental. costs (£) | Incremental QALYs | ICER (£/QALY) | ICER with severity modifier (£/QALY) |
|---|---|---|---|---|---|---|
| **CS base case after correction of errors** | | | | | | |
| BAT | £80,521 | 1.32 | – | – | – | – |
| Ruxolitinib ([redacted] price) | [redacted] | [redacted] | [redacted] | [redacted] | £27,243 | £22,703 |
| **+ Ruxolitinib only different time to NST** | | | | | | |
| BAT | £83,878 | 1.39 | – | – | – | – |
| Ruxolitinib ([redacted] price) | [redacted] | [redacted] | [redacted] | [redacted] | £21,021 | £17,517 |
| **+ Utility cGvHD ≤4 cycles equal to failure-free ≤4 cycles** | | | | | | |
| BAT | £83,878 | 1.39 | – | – | – | – |
| Ruxolitinib ([redacted] price) | [redacted] | [redacted] | [redacted] | [redacted] | £21,010 | £17,508 |
| **+ Disutility AE multiplicative (EAG base case)** | | | | | | |
| BAT | £83,878 | 1.39 | – | – | – | – |
| Ruxolitinib ([redacted] price) | [redacted] | [redacted] | [redacted] | [redacted] | £20,987 | £17,489 |
| **+ 1st line BAT distribution after ruxolitinib for a GvHD** | | | | | | |
| BAT | £83,878 | 1.39 | – | – | – | – |
| Ruxolitinib ([redacted] price) | [redacted] | [redacted] | [redacted] | [redacted] | £23,009 | £19,174 |
| **+ 35% of the patients incurring wastage of ruxolitinib** | | | | | | |
| BAT | £83,878 | 1.39 | – | – | – | – |

| | | | | | | |
|---|---|---|---|---|---|---|
| Ruxolitinib ([redacted] price) | [redacted] | [redacted] | [redacted] | [redacted] | £23,929 | £19,941 |
| **+ Disutility from non-crossover BAT patients for cGvHD, NST** | | | | | | |
| BAT | £83,878 | 1.35 | – | – | – | – |
| Ruxolitinib ([redacted] price) | [redacted] | [redacted] | [redacted] | [redacted] | £24,382 | £20,318 |

Source: Table 2 company's response to DGD

AE, adverse event; aGvHD, acute graft-versus-host-disease; BAT, best available therapy; [redacted] cGvHD, chronic graft-versus-host-disease; CS, company submission; ICER, incremental cost-effectiveness ratio; NST, new systemic treatment; QALY, quality-adjusted life year.

Table 2 presents the results of probabilistic sensitivity analysis (PSA) based on the company new base case. The PSA results are very similar to the deterministic results. The cost-effectiveness acceptability curve (CEAC) (1) shows that ruxolitinib was dominant in [redacted]% of simulations and was cost-effective in [redacted]% and [redacted]% of simulations at a threshold ICER of £20,000 per QALY without and with the severity modifier, respectively, and [redacted]% and [redacted]% of simulations at a threshold ICER of £30,000 per QALY without and with the severity modifier, respectively.

**Table 2 PSA results based on the company new base case (ruxolitinib [redacted] price)**

| Technologies | Total costs | Total QALYs | Incremental. costs | Incremental QALYs | ICER (/QALY) | ICER with severity modifier (/QALY) |
|---|---|---|---|---|---|---|
| BAT | £82,845 | 1.33 | – | – | – | – |
| Ruxolitinib ([redacted] price) | [redacted] | [redacted] | [redacted] | [redacted] | £23,876 | £19,897 |

Source: Table 5 company's response to DGD

BAT, best available therapy; [redacted]; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year

**Figure 1 Cost-effectiveness acceptability curve (ruxolitinib [redacted] price, with and without modifier)**

[redacted]

Source: Figure 5 company's response to DGD

Table 3 shows the full results of the various scenarios that were discussed under comment 3 and 4.

**Table 3: Scenario analyses results, with [redacted] price**

| Scenario | Incremental costs | Incremental QALYs | ICER | ICER with severity modifier |
|---|---|---|---|---|
| Disutility per regression models | [redacted] | [redacted] | £23,929 | £19,941 |
| Disutility in the observed data | [redacted] | [redacted] | £24,097 | £20,081 |
| EAG preference from TA949 | [redacted] | [redacted] | £24,591 | £20,492 |
| All patients incurring wastage of ruxolitinib | [redacted] | [redacted] | £26,122 | £21,768 |

Source: Table 4 company's response to DGD

BAT, best available therapy; [redacted]; cGvHD, chronic graft-versus-host-disease; EAG, external assessment group; FF, failure-free; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TA, technology appraisal.