National Institute for Health and Care Excellence

Health Technology Evaluation

Ruxolitinib for treating acute graft versus host disease refractory to corticosteroids in people aged 12 and over [ID6377]

Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	British Society of Blood and Marrow Transplantation and Cellular Therapy (BSBMTCT)	Appropriate	Thank you for your comment. No action required.
	Royal Marsden Hospital	Yes is appropriate	Thank you for your comment. No action required.
	Leukaemia Care	This topic should be high priority for evaluation. The treatment is standard of care elsewhere.	Thank you for your comment. No action required.

Section	Stakeholder	Comments [sic]	Action
	Anthony Nolan	Anthony Nolan welcomes this evaluation as there is high unmet need for patients with acute GvHD. We would note that acute GvHD affects a relatively small number of patients and that there are very limited treatment options for acute GvHD that does not respond to steroids, so this topic may be appropriate for the highly specialised technology appraisal route.	Thank you for your comment. This topic does not meet the criteria for an HST appraisal and so will be evaluated as an STA.
	Novartis Pharmaceuticals UK Ltd	We agree that the Single Technology Appraisal (STA) process is the most appropriate evaluation route for this topic.	Thank you for your comment. No action required.
Wording	British Society of Blood and Marrow Transplantation and Cellular Therapy (BSBMTCT)	Yes	Thank you for your comment. No action required.
	Royal Marsden Hospital	yes	Thank you for your comment. No action required.
	Leukaemia Care	-	Thank you.
	Anthony Nolan	-	Thank you.

Section	Stakeholder	Comments [sic]	Action
	Novartis Pharmaceuticals UK Ltd	We agree that the wording of the remit is appropriate.	Thank you for your comment. No action required.
Timing issues	British Society of Blood and Marrow Transplantation and Cellular Therapy (BSBMTCT)	Urgent due to case of clinical need and acute nature of indication. Also urgently needed to address inequalities between patients in England and those in devolved nations and ROW, where this agent is SOC for the licensed indication.	Thank you for your comment. No action required.
	Royal Marsden Hospital	Urgent – The REACH 2 randomised trial that demonstrates the improvement of overall response rate and failure free survival of Ruxolitinib against standard of care therapy was published in 2020. we currently are not offering our patients with steroid refractory acute GVHD optimal therapy for GVHD. This impacts on our long term DFS and NRM post HSCT and impacts on QOL of our patients and leads to higher costs for the NHS long term.	Thank you for your comment. No action required.
	Leukaemia Care	GvHD can prevent people who have a transplant from returning to normal activities, having already used significant investment of time and resources from the NHS as well as impacting on the person's quality of life.	Thank you for your comment. No action required.
	Anthony Nolan	Anthony Nolan believes that there is real urgency for new medicines to treat acute GvHD that does not respond to steroids, where there are extremely limited treatment options.	Thank you for your comment. No action required.

Section	Stakeholder	Comments [sic]	Action
		Ruxolitinib had been available on an interim basis during the COVID-19 pandemic but was subsequently withdrawn from funding, adding to the sense of urgency for this evaluation.	
	Novartis Pharmaceuticals UK Ltd	There is a significant unmet need for an effective new treatment option with a favourable safety profile in the management of steroid-refractory (SR)-aGvHD. We are pleased that NICE have been able to schedule the appraisal in a timely manner, following our request to re-open the terminated appraisal. Ruxolitinib has already received its licence from the MHRA for the treatment of patients 12 years or older with aGvHD who have an inadequate response to corticosteroids in March 2022. It was commissioned by NHSE in the UK for the treatment of GvHD in response to the COVID-19 pandemic as a way of reducing hospital attendances [1]. References: NHS England and NHS Improvement. Rapid Policy Statement: Ruxolitinib for acute Graft versus Host Disease. NHSE; 2021.	Thank you for your comment. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	British Society of Blood and Marrow Transplantation	The comments on timing of Acute and Chronic GvHD are significantly outdated. Both are now considered clinico-pathological diagnoses.	Thank you for your comment, the scope has been updated to

Section	Consultee/ Commentator	Comments [sic]	Action
	and Cellular Therapy (BSBMTCT)	Both conditions may occur at any time following transplant, in particular acute pattern GVHD may occur beyond day 100 following the administration of donor lymphocytes or delayed withdrawal of immunosuppression. (reference E. Carreras et al. (eds.), The EBMT Handbook, https://doi.org/10.1007/978-3-030-02278-5_43)	remove reference to timing.
	Royal Marsden Hospital	Acute GvHD usually occurs within 100 days after a HSCT (whereas chronic GvHD usual occurs more than 100 days after).- this is too simplistic, also need to reference overlap and Acute pattern GVHD post DLi.	Thank you for your comment, the scope has been updated to remove reference to timing. Please note that the background section of the scope is only intended to be a brief overview of the condition.
	Leukaemia Care	-	Thank you.
	Anthony Nolan	We suggest amending the background section as follows: - Rephrase the sentence **"*...(GvHD) usually occurs after an allogeneic stem cell transplant…*"** to **"*(GvHD) affects an estimated 35%–50% of hematopoietic stem cell transplant (HSCT) recipients. It occurs when donated cells attack the recipient's own cells."*** (source)	Thank you for your comments. The scope has been updated for clarity.

Section	Consultee/ Commentator	Comments [sic]	Action
		- There is a spelling mistake in the sentence **"...(whereas chronic GvHD usual occurs…"** - Rephrase **"*Acute GvHD is characterised by damage to the...*"** to **"*Acute GvHD can cause damage to…*"** We suggest adding a clearer estimate of mortality due to acute GvHD after HSCT for context. GvHD is a major cause of transplant-related morbidity and mortality.	
	Novartis Pharmaceuticals UK Ltd	The background information currently quotes an outdated version of the European Society for Blood and Marrow Transplantation (ESBMT) guidelines [1]. These were updated recently (January 2024) [2], and the recommendations for SR-aGvHD have changed. The new version of the ESBMT guidelines states that ruxolitinib is strongly recommended as primary treatment in patients with SR-aGvHD. The authors consider the REACH2 RCT to show a large beneficial effect on overall response rate and failure-free survival (FFS), with no relevant increase of undesirable effects [2]. Additionally, it is important to note that Ruxolitinib is indicated for the treatment of patients aged 12 years and older with acute graft versus host disease who have an inadequate response to corticosteroids only, as opposed to "or other systemic therapies", as the background information currently states [3]. References:	Thank you for your comments, the scope has been updated with the latest version of the guidelines.

Section	Consultee/ Commentator	Comments [sic]	Action
		1. Penack O, Marchetti M, Ruutu T, et al. (2020) Prophylaxis and management of graft versus host disease after stem-cell transplantation for haematological malignancies: updated consensus recommendations of the European Society for Blood and Marrow Transplantation. Lancet Haematol. 2020;7(2):e157-e167. 2. Penack O, Marchetti M, Aljurf M, Arat M, Bonifazi F, Duarte RF, Giebel S, Greinix H, Hazenberg MD, Kröger N, Mielke S, Mohty M, Nagler A, Passweg J, Patriarca F, Ruutu T, Schoemans H, Solano C, Vrhovac R, Wolff D, Zeiser R, Sureda A, Peric Z. Prophylaxis and management of graft-versus-host disease after stem-cell transplantation for haematological malignancies: updated consensus recommendations of the European Society for Blood and Marrow Transplantation. Lancet Haematol. 2024 Feb;11(2):e147-e159. doi: 10.1016/S2352-3026(23)00342-3. Epub 2024 Jan 3. PMID: 38184001. 3. MHRA. Summary of Product Characteristics. Microsoft Word - 4141236874865661389_spc-doc.doc (windows.net)	
Population	British Society of Blood and Marrow Transplantation and Cellular Therapy (BSBMTCT)	[Is the population defined appropriately?] yes	Thank you for your comment. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Royal Marsden Hospital	Yes, if you want to comment on % of patients having HSCT from alternative donor source	Thank you for your comment. Please note that the background section of the scope is only intended to be a brief overview of the condition. No action required.
	Leukaemia Care	-	Thank you.
	Anthony Nolan	-	Thank you.
	Novartis Pharmaceuticals UK Ltd	We believe the population has been defined appropriately.	Thank you for your comment. No action required.
Subgroups	British Society of Blood and Marrow Transplantation and Cellular Therapy (BSBMTCT)	[Are there groups within the population that should be considered separately? For example, are there subgroups in which the technology is expected to be more clinically or cost effective? If subgroups have been suggested in the scope, are these appropriate?] No	Thank you for your comment. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Royal Marsden Hospital	n/a	Thank you.
	Leukaemia Care	-	Thank you.
	Anthony Nolan	-	Thank you.
	Novartis Pharmaceuticals UK Ltd	In line with the draft scope, we do not anticipate any subgroups to be considered.	Thank you for your comment. No action required.
Comparators	British Society of Blood and Marrow Transplantation and Cellular Therapy (BSBMTCT)	Yes, CCP: Rx for GvHD following HSCT lists currently commissioned treatments for acute GvHD	Thank you for your comment. No action required.
	Royal Marsden Hospital	Yes – also include Anti-TNF blockade which is used for acute Refractory Gut GVHD in some centres. In the majority of centres the standard second line therapy for Steroid Refactory GVHD is ECP but if there is a delay in starting then the options would be to restart calcineurin inhibition, add in MMF. Sirolimus tends to be third line or beyond.	Thank you for your comments. We note that the NHS clinical commissioning policy states that: 'NHS England has concluded that there is

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			not currently sufficient evidence to support a proposal for the routine commissioning of the following treatments for aGvHD following HSCT: infliximab, etanercept, inolimomab, alemtuzumab, pentostatin or mesenchymal stem cells.' The comparator listed in the scope is established clinical management and is not restrictive. In its deliberations, the committee will consider which treatments represent established clinical management in the NHS. No action required.
	Leukaemia Care	-	Thank you.

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	Anthony Nolan	-	Thank you.
	Novartis Pharmaceuticals UK Ltd	The comparator listed in the draft scope, namely, established clinical management without ruxolitinib, including but not limited to extracorporeal photopheresis and combination therapy with mammalian target of rapamycin inhibitors (for example, sirolimus) and/or mycophenolate mofetil, is appropriate. Established clinical management also includes infliximab, etanercept, and mesenchymal stromal cells (MSC) [1], and anti-thymocyte globulin (ATG) as noted by UK clinicians. References 1. NHS England. Clinical Commissioning Policy: Treatments for Graft versus Host Disease (GvHD) following Haematopoietic Stem Cell Transplantation. 2017 Mar. NHS England » Clinical Commissioning Policy: Treatments for Graft versus Host Disease (GvHD) following Haematopoietic Stem Cell Transplantation	Thank you for your comments. We note that the NHS clinical commissioning policy states that: 'NHS England has concluded that there is not currently sufficient evidence to support a proposal for the routine commissioning of the following treatments for aGvHD following HSCT: infliximab, etanercept, inolimomab, alemtuzumab, pentostatin or mesenchymal stem cells.' The comparator listed in the scope is established clinical management and is not restrictive. In

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			its deliberations, the committee will consider which treatments represent established clinical management in the NHS. No action required.
Outcomes	British Society of Blood and Marrow Transplantation and Cellular Therapy (BSBMTCT)	Yes	Thank you for your comment. No action required.
	Royal Marsden Hospital	also include GVHD free relapse free survival. Day 100 NRM and 1 year NRM.	Thank you for your comments. Failure-free survival and non-relapse mortality have been included in the outcomes list.
	Leukaemia Care	-	Thank you.
	Anthony Nolan	-	Thank you.

Section	Consultee/ Commentator	Comments [sic]	Action
	Novartis Pharmaceuticals UK Ltd	The outcomes listed (complete response, overall response, mortality, adverse effects of treatment, health-related quality of life) are appropriate. However, failure-free survival (FFS) is also a relevant outcome as it was included as a secondary endpoint in the REACH2 trial [1], and was highlighted as such in TA949 [2]. Therefore, FFS should be added to the final scope. References 1. Zeiser R, von Bubnoff N, Butler J, Mohty M, Niederwieser D, Or R, et al. Ruxolitinib for Glucocorticoid-Refractory Acute Graft-versus-Host Disease. N Engl J Med. 2020;382(19):1800-10. 2. Single Technology Appraisal Belumosudil for treating chronic graft versus host disease after 2 or more lines of systemic therapy [ID4021] Committee Papers. 20th March 2023. committee-papers-2 (nice.org.uk)	Thank you for your comments. Failure-free survival and non-relapse mortality have been included in the outcomes list.
Equality	British Society of Blood and Marrow Transplantation and Cellular Therapy (BSBMTCT)	I believe this draft does not need changing to meet these aims and requirements.	Thank you for your comment. No action required.

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	Royal Marsden Hospital	No change needed. Access to Ruxolitinib would improve equality eg there is inequal access to ECP, and patients from lower socio-economic groups are less likely to go for ECP given difficulty in/cost to travel to ECP centre, need to give up working days for ECP.	Thank you for your comment. This issue has been included in the equality impact assessment. The committee will consider relevant equality issues in its deliberations.
	Leukaemia Care	-	Thank you.
	Anthony Nolan	People from a minority ethnic background in the UK who do not have a fully matched related donor are less likely than people from a White background to find a fully matched unrelated donor, and are more likely to receive an HLA mismatched donor. This could contribute to an increased risk of GvHD.	Thank you for your comment. This issue has been included in the equality impact assessment. The committee will consider relevant equality issues in its deliberations.
	Novartis Pharmaceuticals UK Ltd	When receiving a transplant, human leukocyte antigen (HLA) matching is preferred to reduce the risk of GvHD. However, the chance of finding a perfect match is low, especially for some ethnic groups [1]. Mismatched HLA donor grafts can contribute to a higher incidence of GvHD in transplant patients [2], therefore, certain ethnic groups may be more likely to experience aGvHD.	Thank you for your comment. These issues have been included in the equality impact assessment. The committee will consider

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		The current mainstay of SR-aGvHD treatment (ECP) is currently only available in a select few centres in the UK. This means that some patients will need to travel to receive their treatment, which may disadvantage patients who come from disadvantaged socio-economic backgrounds. Given the need for two 2-hour procedures on consecutive days, every 2 or 4 weeks, access may be particularly challenging. 1. HLA (mis)matching in haploidentical transplantation, A. Hyde - HLA (mis)matching in haploidentical transplantation (aml-hub.com) 2. Flowers M, Inamoto Y, Carpenter P, et al. Comparative analysis of risk factors for acute graft-versus-host disease and for chronic graftversus-host disease according to National Institutes of Health consensus criteria. Blood. 2011. 117(11):3214-3219	relevant equality issues in its deliberations.
Other considerations	British Society of Blood and Marrow Transplantation and Cellular Therapy (BSBMTCT)	Potential reduction in use of scarce and expensive resource such as BMT specialist inpatient bed use and scarce specialist resource such as apheresis which proves an alternative therapy, ECP.	Thank you for your comment. No action required.
	Royal Marsden Hospital	-	Thank you.

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	Leukaemia Care	-	Thank you.
	Anthony Nolan	-	Thank you.
	Novartis Pharmaceuticals UK Ltd	-	Thank you.
Questions for consultation	British Society of Blood and Marrow Transplantation and Cellular Therapy (BSBMTCT)	**Would ruxolitinib ever be given in combination with other treatments? If so, which treatments?** Ruxolitinib may be used in combination with immunosuppressive agents such as calcineurin inhibitors or MMF and potentially allow withdrawal of such agents. **Would acute graft-versus-host disease be more likely to occur in people for whom tissue-type matched donors may be more difficult to identify, for example people from a Black, Asian or minority ethnic family background?** Acute GvHD may occur at a higher incidence in those who have mismatched transplants. Those for whom it is more difficult to identify a fully matched donor, such as those from a minority ethnic background or from mixed ethnic heritage may therefore currently be more at risk.	Thank you for your comment. No action required. Thank you for your comment. This issue has been included in the equality impact assessment. The committee will consider relevant equality issues in its deliberations.

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	Royal Marsden Hospital	**Where do you consider ruxolitinib will fit into the existing care pathway for acute graft versus host disease?** As an option for 2nd line therapy (or beyond) of Acute steroid refractory GVHD (ECP should also still be available as 2nd line option).	Thank you for your comment. No action required.
		Would ruxolitinib ever be given in combination with other treatments? If so, which treatments? Yes is commonly given with corticosteroids/MMF/CSA.	Thank you for your comment. No action required.
		Would acute graft-versus-host disease be more likely to occur in people for whom tissue-type matched donors may be more difficult to identify, for example people from a Black, Asian or minority ethnic family background? Yes more likely to have a mismatched unrelated donor or alternative donor so higher risk of steroid refactory GVHD.	Thank you for your comment. This issue has been included in the equality impact assessment. The committee will consider relevant equality issues in its deliberations.
		Do you consider that the use of ruxolitinib can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? If the main comparator is ECP – then Ruxolitinib does not require central venous access or travel to an ECP centre (or specialist nurse travelling to a hospital to do inpatient ECP). Also steroid refactory GVHD – can lead to	Thank you for your comment. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		prolonged hospital and ICU admissions, decrement in patients performance status, huge increased risk of steroid related side effects (obesity, osteoporeosis, infectious complications, diabetes, myopathy)	
	Leukaemia Care	-	Thank you.
	Anthony Nolan	**Do you consider that the use of ruxolitinib can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** One of the issues that may not be captured in the QALY calculations is the ability to take ruxolitinib orally and at home, which has a significant benefit to patients' quality of life. The ability to receive an oral treatment at home would also be of benefit to NHS capacity. These factors should be considered as part of this evaluation.	Thank you for your comment. No action required.
	Novartis Pharmaceuticals UK Ltd	**Where do you consider ruxolitinib will fit into the existing care pathway for acute graft versus host disease?** In line with its marketing authorisation and the draft scope, ruxolitinib should be used in patients aged 12 years and above with steroid-refractory acute graft-versus-host disease who have inadequate response to corticosteroids. **Would ruxolitinib ever be given in combination with other treatments? If so, which treatments?** As per the REACH2 trial, ruxolitinib may be given in combination with corticosteroids, and calcineurin inhibitors (CNI). However, steroids will be	Thank you for your comment. No action required. Thank you for your comment. No action required.

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		tapered over time. According to UK clinicians, mycophenolate mofetil (MMF) may also be given alongside ruxolitinib. **Would ruxolitinib be a candidate for managed access?** We do not consider ruxolitinib as a candidate for managed access, as there are no on-going trials which address areas of clinical uncertainty. **Do you consider that the use of ruxolitinib can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** In the REACH2 trial, patients in the ruxolitinib arm were able to taper corticosteroids. More patients in the ruxolitinib arm (43.5%; 95% CI: 35.5, 51.7) had completely tapered off corticosteroids than in BAT arm (31.6%; 95% CI:24.4, 39.6) [2]. Steroids have many well documented side effects, including immunosuppression, hyperglycaemia, and osteopenia [3], and the long-term benefits of corticosteroid reduction are unlikely to be adequately captured in the economic analysis presented in the company submission. UK clinicians have confirmed that ECP is the most frequently used treatment in SR-aGvHD patients. ECP is a cell-based immunomodulatory therapy that involves collecting leukocytes from peripheral blood. These cells are exposed to a photosensitizing agent, 8-methoxypsoralen, and are then treated with ultraviolet (UV) radiation, after which they are re-infused [1]. ECP involves two 2-hour procedures on consecutive days, every 2 or 4 weeks. This	Thank you for your comment. No action required. Thank you for your comment. No action required.

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		procedure puts substantial stress on the patients and their caregivers, which may be difficult to capture in the QALY calculation. By contrast, ruxolitinib is an oral therapy. Previous appraisals have noted the challenge in adequately capturing the benefit of oral administration vs. intravenous line (IV) in the economic analysis [3,4]. Receiving an oral therapy may be perceived by patients as less burdensome and disruptive to their lives. Some patients may also perceive an oral treatment as less invasive compared with ECP. These potential benefits may not be captured in the QALY calculation. Additionally, as ECP is only available in a few centres in the UK, this means that those patients who can, must travel to receive their treatment. This increases their risk of infection. Avoiding these additional infections cannot be captured in the QALY calculation. An effective oral treatment may also have benefits on workplace productivity which are not captured due to the healthcare system perspective of the analysis. Substantial time off work is required to receive ECP treatment. References: 1. Dignan FL, Clark A, Amrolia P, Cornish J, Jackson G, Mahendra P, Scarisbrick JJ, Taylor PC, Hadzic N, Shaw BE, Potter MN; Haemato-oncology Task Force of British Committee for Standards in Haematology; British Society for Blood and Marrow Transplantation. Diagnosis and management of acute graft-versus-host disease. Br J Haematol. 2012 Jul;158(1):30-45. doi: 10.1111/j.1365-2141.2012.09129.x. Epub 2012 Apr 26. PMID: 22533831.	

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		2. Zeiser R, von Bubnoff N, Butler J, Mohty M, Niederwieser D, Or R, et al. Ruxolitinib for Glucocorticoid-Refractory Acute Graft-versus-Host Disease. N Engl J Med. 2020;382(19):1800-10. 3. NICE TA921. Ruxolitinib for treating polycythaemia vera. October 2023. Overview | Ruxolitinib for treating polycythaemia vera | Guidance | NICE 4. NICE TA898. Dabrafenib plus trametinib for treating BRAF V600 mutation-positive advanced non-small-cell lung cancer. June 2023. Overview | Dabrafenib plus trametinib for treating BRAF V600 mutation-positive advanced non-small-cell lung cancer | Guidance | NICE	
Additional comments on the draft scope	British Society of Blood and Marrow Transplantation and Cellular Therapy (BSBMTCT)	It is the opinion of the BSBMTCT Complications subcommittee that the inability to access Ruxolitinib in England for the treatment of steroid refractory acute GvHD (SR aGvhD) has resulted in England becoming a significant outlier compared to Scotland and Wales, and the rest of the world. Ruxolitinib is the internationally recognised standard of care for SR aGvHD, evidenced by the best current randomised prospective data in the field, and reflected in recent guidelines from the EBMT, and pending updates to British guidelines. A real world analysis performed by the British Pharmacy group of outcomes for patients who received ruxolitinib via temporary commissioning during the COVID pandemic revealed similar outcomes to those included in the REACH 2 trial, and it is imperative that this inequality of access across the UK is addressed promptly, in order to optimise patient outcomes following allogeneic stem cell transplantation.	Thank you for your comment. No action required.
	Royal Marsden Hospital	-	Thank you.

Section	Consultee/ Commentator	Comments [sic]	Action
	Leukaemia Care	-	Thank you.
	Anthony Nolan	-	Thank you.
	Novartis Pharmaceuticals UK Ltd	-	Thank you.

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

- Lymphoma Action