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:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Novartis Pharmaceuticals:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**
   a. Appendix

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Anthony Nolan & Leukaemia Care – endorsed by patient expert, Elsa Bennett
   b. British Society for Blood and Marrow Transplantation and Cellular Therapy
   c. NHS England Blood and Marrow Transplantation Clinical Reference Group – co-authored by clinical expert Dr Fiona Dignan

4. **External Assessment Report** prepared by Kleijnen Systematic Reviews

5. **External Assessment Report – factual accuracy check**

6. **Statements from experts:**
   a. Dr. Fiona Dignan, Consultant Haematologist and National Specialty Advisor for Blood and Marrow Transplantation CRG – clinical expert, nominated by NHSE
   b. Elsa Bennett – patient expert, nominated by Anthony Nolan
   c. Kenneth Dawson – patient expert, nominated by Anthony Nolan

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

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 [ID6377]

Consolidated Document B
Company evidence submission

July 2024

File name	Version	Contains confidential information	Date
ID6377_Ruxolitinib_SR-aGvHD_Document B_final_[CON].docx	2.0	Yes (CiC)	1st July 2024

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Abbreviations

1L	First-line
2L	Second-line
3L	Third-line
AE	Adverse event
aGvHD	Acute graft-versus-host disease
AIC	Akaike information criteria
alloSCT	Allogeneic stem cell transplantation
ALL	Acute lymphoblastic leukaemia
AML	Acute myeloid leukaemia
APC	Antigen-presenting complex
ATG	Anti-thymocyte globulin
BAT	Best available therapy
BIC	Bayesian information criteria
BID	Twice a day
BOR	Best overall response
BSA	Body surface area
BSBMT	British Society for Blood and Marrow Transplantation
BSBMTCT	British Society for Blood and Marrow Transplantation and Cellular Therapy
[redacted]	[redacted]
CADTH	Canadian Agency for Drugs and Technologies in Health
CEAC	Cost-effectiveness acceptability curve
CEP	Cost-effectiveness plane
cGvHD	Chronic graft-versus-host-disease
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CNI	Calcineurin inhibitor
COVID-19	Coronavirus disease 2019
CR	Complete response
DAMP	Damage-associated molecular pattern
DCO	Data cut-off
DOR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EAG	External Assessment Group
EBMT	European Society for Blood and Marrow Transplantation
ECP	Extracorporeal photopheresis
EFS	Event-free survival

eMIT	eMIT, electronic market information tool
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core
EOS	End of study
EOT	End of treatment
EQ-5D-5L	EuroQol five-dimension five-level
FACT-BMT	Functional Assessment of Cancer Therapy - Bone Marrow Transplantation
FACT-G	Functional Assessment of Cancer Therapy-General
FAS	Full analysis set
FF	Failure-free
FFS	Failure-free survival
GI	Gastrointestinal
GvHD	Graft-versus-host-disease
HCRU	Healthcare resource use
HLA	Human leukocyte antigen
HR	Hazard ratio
HRQoL	Health-related quality of life
HSE	Health Survey for England
HSUV	Health state utility value
IFN	Interferon
IL	Interleukin
IPD	Individual patient data
IQR	Interquartile range
IRT	Interactive Response Technology
JAK1	Janus kinase 1
JAK2	Janus kinase 2
KM	Kaplan-Meier
LFT	Liver function tests
MDS	Myelodysplastic syndrome
MHC	Major histocompatibility complex
MMF	Mycophenolate mofetil
MPN	Myeloproliferative neoplasm
MRU	Medical resource utilisation
MSC	Mesenchymal stromal cells
MSM	Multi-state model
mTOR	Mammalian target of rapamycin
MTX	Methotrexate
NHS	National Health Service
NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence

NIHR	National Institute for Health and Care Research
NRM	Non-relapse mortality
ORR	Overall response rate
OS	Overall survival
PAMP	Pathogen-associated molecular pattern
PartSA	Partitioned survival model
PBAC	Pharmaceutical Benefits Advisory Committee
PR	Partial response
PRO	Patient-reported outcomes
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PT	Preferred term
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RSV	Respiratory syncytial virus
RWE	Real world evidence
SAE	Serious adverse event
SD	Standard deviation
SF-36	36-item Short Form Health Survey
SFID-SCT	Symptom, Frequency, Intensity, and Distress Questionnaire for Stem Cell Transplantation
SLR	Systematic literature review
SoC	Standard of care
TAS	Therapeutic Apheresis Services
Tc	T cytotoxic
Th	T helper
TSD	Technical Support Document
VAS	Visual analogue score
VBA	Visual Basic for Applications
WBC	White blood cell
WTP	Willingness-to-pay

B.1. Decision problem, description of the technology and clinical care pathway

Acute graft-versus-host-disease (aGvHD) is a serious complication of allogeneic stem cell transplantation (alloSCT) (1-4)

- AlloSCT is the only potentially curative immunotherapy for life-threatening conditions such as acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL) (accounting for 36% and 16% of alloSCT cases, respectively) (5, 6)
- Acute GvHD is a common complication of alloSCT, and occurs when the graft's immune cells recognise the host as foreign and attack the recipient's body cells (4)
- Acute GvHD is characterised by systemic inflammation and ultimately, tissue destruction affecting multiple organs, particularly the gut, liver, lungs, bone marrow, thymus, and skin
- In 2022, there were 1,535 allogeneic transplants in the United Kingdom (UK) (7)
- According to the British Society for Blood and Marrow Transplantation (BSBMT) Outcomes Register, the rate of aGvHD for all adult allograft recipients ranges from 34-48%, depending on stem cell source (8), although UK clinical experts confirmed this figure is closer to 48% on average (9)

Acute GvHD is one of the major causes of morbidity and mortality following alloSCT, and is associated with compromised quality of life and a high economic burden (10, 11)

- Typically, steroids are the first-line (1L) treatment for aGvHD (12), but around 50% of patients are refractory and will require additional therapy (9)
- Patients with steroid-refractory acute GvHD (SR-aGvHD) have poor survival, with only 25% of patients alive 2 years after diagnosis, decreasing further to 10% at 4 years (13, 14)
- Acute GvHD occurs primarily in the skin, gastrointestinal (GI) tract and liver (15); skin is usually the first organ affected, with a maculopapular rash and, in severe cases, blistering, ulceration and epidermal necrosis (1, 2, 16). Involvement of the GI tract can be severe, with up to ten litres of diarrhoea per day and rectal bleeding (2, 16)
- The heavy symptom burden experienced by patients with aGvHD following alloSCT significantly affects their health-related quality of life (HRQoL) (11, 17, 18), in terms of physical (p=0.003), emotional (p=0.005) and functional well-being (p=0.003), compared with controls
- There is a high economic burden associated with aGvHD. The mean cost of readmission is higher in patients with GvHD (£28,860) than in non-GvHD patients (£13,405; p=0.002). The direct costs arise from treatment of the disease or of infections related to immunosuppressive therapy and relate primarily to hospitalisation, drug therapy, and radiology (10)

Patients with steroid-refractory aGvHD (SR-aGvHD) have a high unmet need for an effective, well-tolerated, and convenient treatment option

- Extracorporeal photopheresis (ECP) is currently the mainstay of second-line (2L) treatment for SR-aGvHD (9, 19)
- According to the National Health Service England (NHSE), there is sufficient evidence to support routine commissioning of ECP only for the 2L treatment of aGvHD in patients who are unsuitable for, are steroid-dependent or show incomplete response to 1L treatment (12)
- According to UK clinical experts, various treatments are being used off-label for patients with SR-aGvHD to varying extents (9), however, they have been evaluated in only small, retrospective, and non-comparative trials (20-25), and they have a low perceived effectiveness according to UK clinical experts.

Ruxolitinib is an inhibitor of the Janus kinases (JAK) 1 and JAK2 that is administered orally

- The European Society for Blood and Marrow Transplantation (EBMT) guidelines recommend ruxolitinib as the primary treatment for SR-aGvHD (26)
- The British Society of Blood and Marrow Transplantation and Cellular Therapy (BSBMTCT) strongly recommend that ruxolitinib should be made available equitably across the UK for patients with SR-GvHD (27)
- Ruxolitinib received a UK marketing authorisation from the Medicines and Healthcare products Regulatory agency (MHRA) in March 2022 for the treatment of patients 12 years and older who have inadequate response to corticosteroids (28). It is currently not recommended by NICE due to termination of TA839 (29).
- Ruxolitinib was commissioned by the NHSE in the UK for the treatment of aGvHD in response to the Coronavirus disease 2019 (COVID-19) pandemic as a way of reducing hospital attendances (30).

B.1.1. Decision problem

The objective of this appraisal is to determine the clinical and cost-effectiveness of ruxolitinib for the treatment of steroid-refractory acute graft-versus-host-disease (SR-aGvHD) in patients 12 years and older who have an inadequate response to corticosteroids. The submission covers the technology's full marketing authorisation for this indication. The decision problem addressed in this submission is provided in Table 1, which outlines any differences from the National Institute for Health and Care Excellence (NICE) final scope (31).

Table 1: The decision problem

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People aged 12 years and older with acute graft versus host disease who have inadequate response to corticosteroids	As per final scope	In line with final scope
Intervention	Ruxolitinib	As per final scope	In line with final scope
Comparator(s)	Established clinical management without ruxolitinib, including but not limited to: • Extracorporeal photopheresis • Combination therapy with mammalian target of rapamycin inhibitors (for example, sirolimus) and/or mycophenolate mofetil	As per final scope	In line with final scope
Outcomes	The outcome measures to be considered include: • Response to treatment (including complete response and overall response) • Mortality (including non-relapse mortality) • Failure-free survival • Adverse effects of treatment • Health-related quality of life.	As per final scope	In line with final scope
Special considerations including issues related to equity or equality	N/A	ECP availability is limited to five therapeutic apheresis services (TAS) units in England, and a limited number of hospital trusts providing ECP services independently. This means patients with aGvHD must travel to	Issues related to ECP and ruxolitinib access were raised by UK clinical experts consulted as part of this submission (9)

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
		receive treatment, thereby increasing their risk of infections. Furthermore, eligibility for ECP also depends on patients having good venous access and being haematologically stable, therefore not all patients are able to receive this treatment option (9). Some centres in England will use their own budgets to enable patient access to ruxolitinib. Additionally, some patients self-fund or use private healthcare (9). This creates inequity of access to ruxolitinib in patients with GvHD across England. In Wales and Scotland, patients have access to ruxolitinib, which creates inequity of access across the UK.	

Abbreviations: aGvHD, acute graft-versus-host disease; alloSCT, allogeneic stem cell transplant; ECP, extracorporeal photopheresis; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; TAS, therapeutic apheresis services; UK, United Kingdom.

B.1.2. Description of the technology being evaluated

The summary of product characteristics is provided in Appendix C. A description of the technology being evaluated is shown in Table 2.

Table 2: Technology being evaluated

UK approved name and brand name	Ruxolitinib (Jakavi®)
Mechanism of action	Ruxolitinib is a potent, selective, and orally bioavailable inhibitor of the tyrosine kinases Janus kinase 1 (JAK1) and 2 (JAK2), which initiate cytokine-triggered signalling events (32). Ruxolitinib inhibits the signalling of several proinflammatory cytokines such as interleukin-1 (IL-1), IL-6, tumour necrosis factor (TNF)-α, and interferon (IFN)-γ that are involved in aGvHD pathogenesis and associated with inflammation, tissue damage, and fibrosis. Furthermore, ruxolitinib may prevent GvHD progression due to its ability to impair differentiation, maturation, and cytokine production of dendritic cells (33)
Marketing authorisation/CE mark status	Ruxolitinib has a UK marketing authorisation from the MHRA (granted in March 2022) for the treatment of patients aged 12 years and older with acute graft versus host disease who have inadequate response to corticosteroids (28)

Indications and any restriction(s) as described in the summary of product characteristics	Ruxolitinib is already licensed in the following indications:
	• Myelofibrosis (MF)
	Ruxolitinib is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis.
	• Polycythaemia vera (PV)
	Ruxolitinib is indicated for the treatment of adult patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea.
	• Graft versus host disease (GvHD)
	Ruxolitinib is indicated for the treatment of patients aged 12 years and older with acute graft versus host disease who have inadequate response to corticosteroids.
	Ruxolitinib is indicated for the treatment of patients aged 12 years and older with chronic graft versus host disease who have inadequate response to corticosteroids.
	
	Based on the SmPC, contraindications include:
	• Hypersensitivity to ruxolitinib or any of the following excipients:
	  • Cellulose, microcrystalline
	  • Magnesium stearate
	  • Silica, colloidal anhydrous
	  • Sodium starch glycolate (Type A)

<table>
<tr><td></td><td>

Povidone K30
Hydroxypropylcellulose 300 to 600 cps
Lactose monohydrate

Pregnancy and lactation

</td></tr>
<tr><td>Method of administration and dosage</td><td>
Ruxolitinib is administered orally. The recommended starting dose of ruxolitinib in acute GvHD is 10 mg given orally twice daily (28).

Dose reductions and temporary interruptions of treatment may be needed in patients with thrombocytopenia, neutropenia, or elevated total bilirubin after standard supportive therapy including growth factors, anti-infective therapies and transfusions. One dose level reduction step is recommended (10 mg twice daily to 5 mg twice daily or 5 mg twice daily to 5 mg once daily). In patients who are unable to tolerate ruxolitinib at a dose of 5 mg once daily, treatment should be interrupted. Detailed dosing recommendations are provided in Table 3.

Table 3: Dosing recommendations for GvHD patients with thrombocytopenia, neutropenia, or elevated total bilirubin
<table>
<tr><th>Laboratory parameter</th><th>Dosing recommendation</th></tr>
<tr><td>Platelet count <20,000/mm^3</td><td>Reduce ruxolitinib by one dose level. If platelet count ≥20,000/mm^3 within seven days, dose may be increased to initial dose level, otherwise maintain reduced dose</td></tr>
<tr><td>Platelet count <15,000/mm^3</td><td>Hold ruxolitinib until platelet count ≥20,000/mm^3, then resume at one lower dose level</td></tr>
<tr><td>ANC ≥500/mm^3 to <750/mm^3</td><td>Reduce ruxolitinib by one dose level. Resume at initial dose level if ANC >1,000/mm^3</td></tr>
<tr><td>ANC <500/mm^3</td><td>Hold ruxolitinib until ANC >500/mm^3, then resume at one lower dose level. If ANC >1,000/mm^3, dosing may resume at initial dose level.</td></tr>
<tr><td rowspan="3">Total bilirubin elevation, no liver GvHD</td><td>>3.0 to 5.0 x ULN: Continue ruxolitinib at one lower dose level until ≤3.0 x ULN</td></tr>
<tr><td>>5.0 to 10.0 x ULN: Hold ruxolitinib up to 14 days until total bilirubin ≤3.0 x ULN. If total bilirubin ≤3.0 x ULN dosing may resume at current dose. If not ≤3.0 x ULN after 14 days, resume at one lower dose level</td></tr>
<tr><td>>10.0 x ULN: Hold ruxolitinib until total bilirubin ≤3.0 x ULN, then resume at one lower dose level.</td></tr>
<tr><td>Total bilirubin elevation, liver GvHD</td><td>>3.0 x ULN: Continue ruxolitinib at one lower dose level until total bilirubin ≤3.0 x ULN</td></tr>
</table>
When ruxolitinib is administered with dual inhibitors of CYP2C9 and CYP3A4 enzymes (e.g. fluconazole) in MF, PV or GvHD patients, the unit dose of ruxolitinib should be reduced by approximately 50%,
</td></tr>
</table>

	to be administered twice daily. The concomitant use of ruxolitinib with fluconazole (doses greater than 200 mg daily) should be avoided. The recommended starting dose for GvHD patients with severe renal impairment is 5 mg twice daily. Patients should be carefully monitored with regard to safety and efficacy during ruxolitinib treatment. In patients with mild, moderate or severe hepatic impairment not related to GvHD, the starting dose of ruxolitinib should be reduced by 50%. In patients with GvHD liver involvement and an increase of total bilirubin to >3 x ULN, blood counts should be monitored more frequently for toxicity and a dose reduction by one dose level may be considered. In GvHD, tapering of ruxolitinib may be considered in patients with a response and after having discontinued corticosteroids. A 50% dose reduction of ruxolitinib every two months is recommended. If signs or symptoms of GvHD reoccur during or after the taper of ruxolitinib, re-escalation of treatment should be considered.
Additional tests or investigations	Before initiating therapy with ruxolitinib, a complete blood cell count, including a white blood cell count differential, must be performed. Thereafter, a complete blood count, including a WBC count differential, should be performed every 2–4 weeks until ruxolitinib doses are stabilised, and then as clinically indicated.
List price and average cost of a course of treatment	List price for 5 mg tablets: £1,428.00 per pack of 56 List price for 10 mg tablets: £2,856.00 per pack of 56 List price for 15 mg tablets: £2,856.00 per pack of 56 List price for 20 mg tablets: £2,856.00 per pack of 56 The expected average cost of a course of treatment for ruxolitinib at list price is £[redacted] reflecting a modelled mean of [redacted] Document B, Section B.3.5.1.3
Patient access scheme (if applicable)	[redacted] Ruxolitinib is provided to the NHS with a [redacted] discount off the list price, and this price has been included in the economic analysis of this submission.

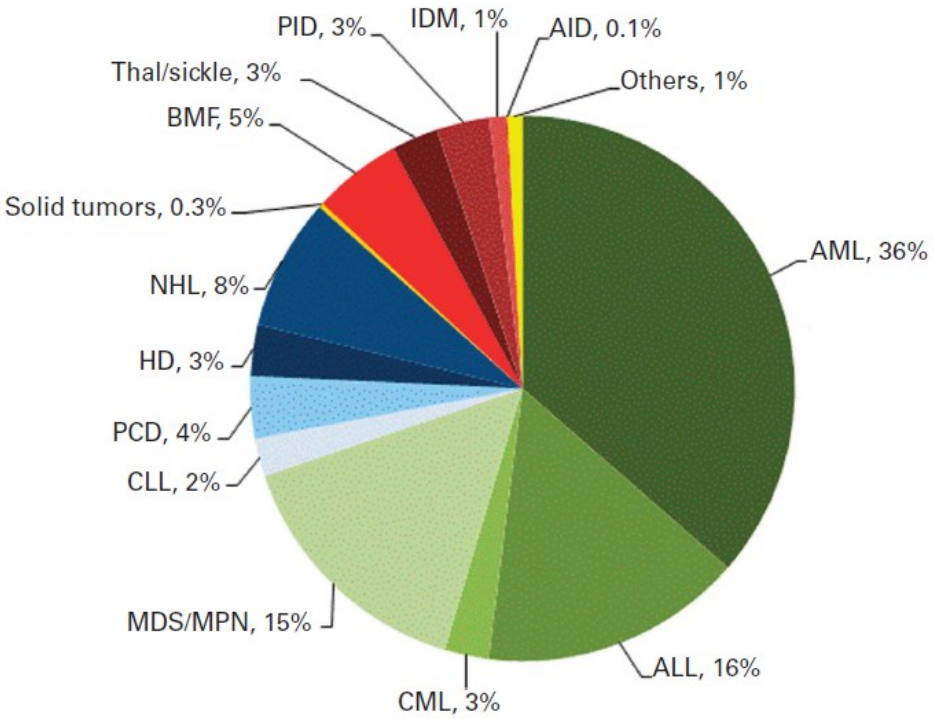
Abbreviations: aGvHD, acute graft-versus-host-disease; ANC, absolute neutrophil count; [redacted] CE, conformité européenne; CHMP, Committee for Medicinal Products for Human Use; CYP2C9, cytochrome P450, family 2, subfamily C, member 9; CYP3A4, cytochrome P450, family 3, subfamily A, member 4; EMA, European Medicines Agency; ; IFN-γ, interferon- γ; IL-1, interleukin-1; IL-6, interleukin-6; JAK1, Janus kinase 1; JAK2, Janus kinase 2; MF, myelofibrosis; MHRA, Medicines and Healthcare products Regulatory agency; NHS, National Health Service; PV, polycythaemia vera; SmPC, summary of product characteristics; UK, United Kingdom; ULN, upper limit of normal; WBC, white blood cell count.

B.1.3. Health condition and positioning of the technology in the treatment pathway

B.1.3.1. Disease overview

Graft-versus-host-disease (GvHD) is a rare disease, and a serious complication occurring in patients who undergo an allogeneic (from a donor) stem cell transplant (alloSCT) (1-4). AlloSCT is the only potentially curative immunotherapy for diseases with poor prognoses such as acute myeloid leukaemia (AML), acute lymphoblastic leukaemia (ALL), myelodysplastic syndrome (MDS) and myeloproliferative neoplasms (MPNs), and non-malignant disorders (Figure 1) (5, 6).

Figure 1: Relative proportions of indications for alloSCT



Source: Passweg et al, 2016 (5).
Abbreviations: AID, autoimmune disease; ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; BMF, bone marrow failure; CLL, chronic lymphocytic leukaemia; CML, chronic myeloid leukaemia; HD, Hodgkin's disease; IDM, inherited disorder of metabolism; MDS/MPN, myelodysplastic syndrome/myeloproliferative neoplasm; NHL, non-Hodgkin's lymphoma; PCD, plasma cell disorder; PID, primary immune deficiency.

GvHD occurs when the graft's immune cells recognise the host as foreign and attack the recipient's body cells, and is the primary cause of morbidity and non-relapse mortality (NRM) in alloSCT recipients (4, 34). GvHD can be acute (aGvHD) or chronic (cGvHD). Although similar, these conditions involve distinct pathological processes and vary in presentation (15, 35). Traditionally, aGvHD had been defined as occurring within 100 days of alloSCT, and cGvHD as arising after 100 days (35, 36) but in 2005, the National Institutes of Health issued

a consensus document stating that no time limit should be set for the diagnosis of cGvHD (37). The distinction between acute and chronic GvHD is now based on clinical manifestations, specific diagnostic criteria and when available, tissue pathology (35). Acute GvHD primarily affects the skin, liver and gastrointestinal (GI) tract, whereas cGvHD can affect any organ in the body (16). Acute GvHD is characterised by systemic inflammation and ultimately, tissue destruction affecting multiple organs (15, 35).

B.1.3.2. Pathophysiology

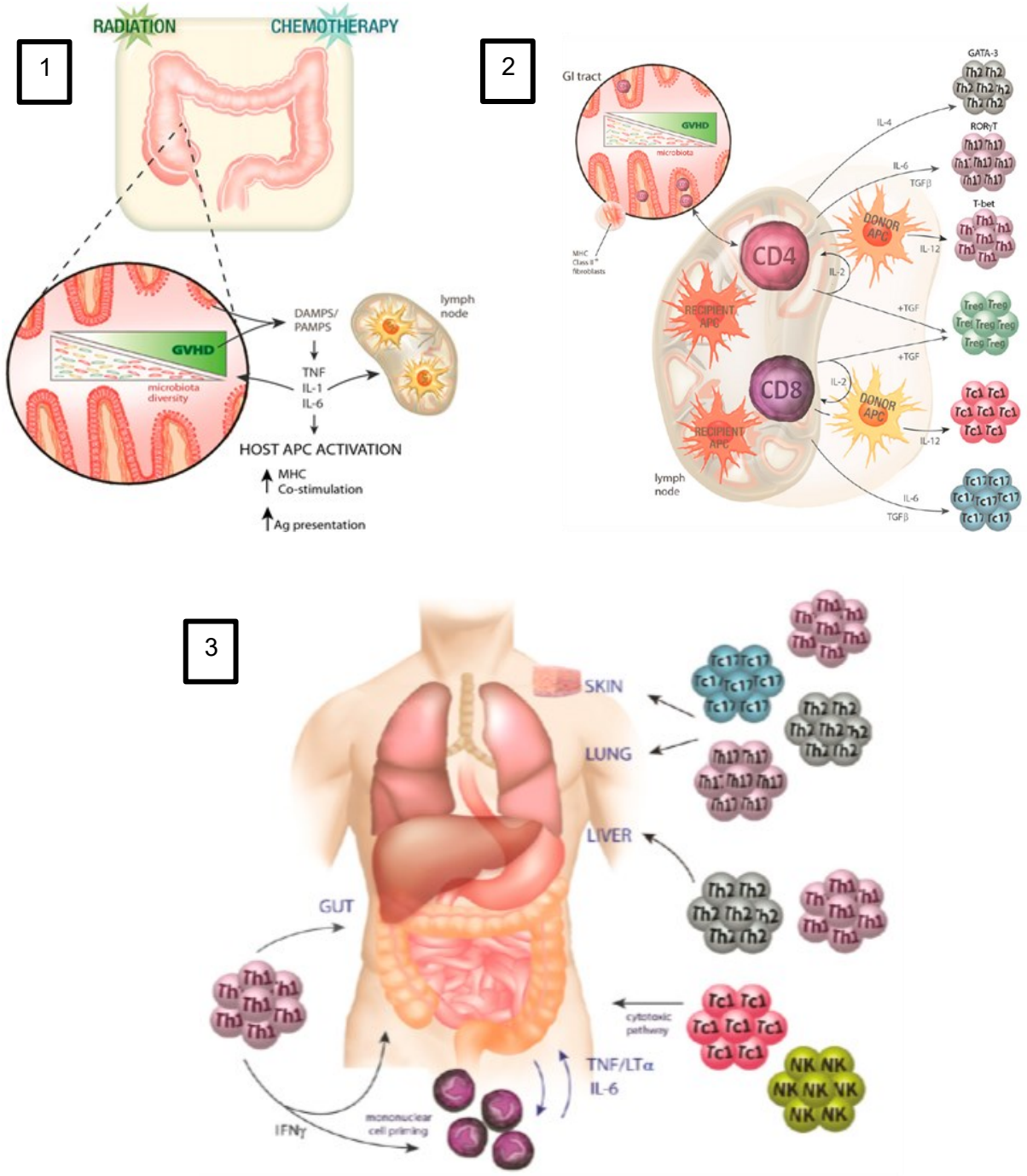
The pathophysiology of aGvHD involves strong inflammatory components and occurs over three phases (Figure 2) that lead to tissue damage in the gut, skin, and liver (15):

- Phase 1: Transplant conditioning and inflammation. Following conditioning (radiation and/or chemotherapy prior to alloSCT), the integrity of the gastrointestinal (GI) mucosa becomes compromised allowing the release of danger-associated molecular patterns (DAMP) and pathogen-associated molecular patterns (PAMP), which in turn promote the production of proinflammatory cytokines (tumour necrosis factor [TNF], interleukin [IL]-1 and IL-6) from recipient cells. These cytokines contribute to host antigen-presenting complex (APC) activation in the gut and lymphoid tissue. GvHD impacts on the gut microbiota, reducing its diversity with a loss of enteric commensal organisms and an outgrowth of pathogenic microbes that further exacerbates the pathological DAMP/PAMP cascade

- Phase 2: Donor T cell priming and differentiation. Donor CD4 T cells contained within the graft are activated by the inflammatory milieu early after conditioning, facilitating their rapid access to the gut and lymphoid tissue. Once in the gut, major histocompatibility complex (MHC) class II–expressing recipient APCs can initiate priming to host antigens and in lymphoid tissue. Activation in the presence of various cytokines instructs T-cell differentiation along specific lineage pathways

- Phase 3: The effector phase (tissue apoptosis). Inflammatory cytokines (interferon [IFN]-g, TNF, lymphotoxin, and IL-6) mediate apoptosis in target tissues, particularly within the gut. Donor T helper (Th)1/ T cytotoxic (Tc)1, Th2/Tc2, and Th17/Tc17 cells elicit GvHD with tissue-specific patterns. Cytolytic T and natural killer (NK) cells mediate antigen-dependent killing of target tissues via the perforin/granzyme and TNF member pathways.

Figure 2: The three phases of aGvHD pathogenesis



Source: Markey et al, 2014 (15).
Abbreviations: Ag, antigen; aGvHD, acute graft-versus-host-disease; APC, antigen-presenting complex; DAMPS, damage-associated molecular patterns; GI, gastrointestinal; GvHD, graft-versus-host disease; IFN, interferon; IL, interleukin; LT, lymphotoxin; MHC, major histocompatibility complex; NK, natural killer; PAMP, pathogen-associated molecular pattern; TGF, transforming growth factor; Tc, T cytotoxic, Th, T helper; TNF, tumour necrosis factor; Treg, T regulatory.

The overall grading of aGvHD (I–IV) depends mostly on organ involvement and decrease in clinical performance (38). Each organ is staged from 0 to 4 and the resultant stages are combined to provide an overall grade (Table 4).

Table 4: Staging and grading of aGvHD

Stage	Skin based on maculopapular rash	Liver based on bilirubin	GI based on quantity of diarrhoea
+	<25% of surface	34–50 µmol/L	500–1000 mL
++	25–50% of surface	51–102 µmol/L	1001–1500 mL
+++	Generalised erythroderma	103–255 µmol/L	>1500 mL
++++	Generalised erythroderma with bullae and desquamation	>255 µmol/L	Severe abdominal pain with and without ileus
Grade			
I	Skin + to ++		
II	Skin + to +++, GI, and/or liver + Mild decrease in performance		
III	Skin ++ to +++, GI, and/or liver ++ to +++ Marked decrease in clinical performance		
IV	Skin ++ to ++++, GI, and/or liver ++ to ++++ Extreme decrease in clinical performance		

Abbreviations: aGvHD, acute graft-versus-host-disease; GI, gastrointestinal.

B.1.3.3. Epidemiology

Derivation of the population in England eligible for treatment with ruxolitinib is provided in Table 5. There is a lack of recent incidence data for aGvHD in England, therefore in order to calculate the eligible population, data from the British Society of Blood and Marrow Transplantation and Cellular Therapy (BSBMTCT) regarding total allogeneic transplants in the UK was used, along with applying several assumptions as described in this section.

The latest data from BSBMTCT report that in 2022, there were 1,535 total allogeneic transplants in the UK (7). However, the data did not report how many of those 1,535 transplants were performed in England. Therefore, based on the 2015 BSBMTCT data, which reported that there were 1,553 allogeneic transplants in the UK, of which 1,411 were in England (i.e. 90.85% of UK transplants were performed in England) (8), this rate was applied to the 2022 transplant number to get the total number of allogeneic transplants performed in England, as seen in the first row of Table 5 (1,535 * 0.9085 = 1,395).

The most recent British Society of Blood and Marrow Transplantation (BSBMT) Report to Specialist Commissioners identified that the rate of aGvHD (all grades) for all adult allograft recipients ranged from 34–48% depending on stem cell source (2,996 patients, 2009–2014 cohort) (8). Feedback from UK clinical experts confirmed it is likely these figures have not

changed significantly, and are likely to be closer to 48% on average (9). This rate was applied to the total number of allogeneic transplants performed in England to get the number of yearly cases of aGvHD, as seen in the second row of Table 5 (1,395 * 0.48 = 670).

Typically, steroids are the first-line (1L) treatment for aGvHD (12), but they are associated with significant side-effects such as hyperglycaemia, hypertension, insomnia, labile mood, gastritis, osteopenia, avascular bone necrosis, myopathy, impaired wound healing, and secondary adrenal insufficiency (39). Like other immunosuppressive treatments, corticosteroid use is also associated with an increased risk of viral reactivation and opportunistic infections (39, 40). UK clinical experts confirmed that 50% patients with aGvHD will become steroid-refractory (9). This rate was applied to the total number of aGvHD cases in England, as seen in the third row of Table 5 (670 * 0.50 = 335). Therefore, there are approximately 335 cases of SR-aGvHD in England per year.

Table 5: Patient population eligible for treatment with ruxolitinib in current year

	Proportion	Number of patients	Source
Number of allogeneic transplants in England per year	–	1,395	BSBMTCT (7, 8)
Annual incidence of aGvHD in England	48%	670	Expert opinion
Annual incidence of SR-aGvHD in England	50%	335	Expert opinion

Abbreviations: aGvHD, acute graft-versus-host-disease; BSBMTCT, British Society of Blood and Marrow Transplantation and Cellular Therapy; SR-aGvHD, steroid-refractory acute graft-versus-host-disease.

B.1.3.4. Disease burden

B.1.3.4.1. Clinical burden

It is important to note that patients with GvHD have already faced extensive challenges through haematological and immunological disease, followed by a life-threatening transplant. As mentioned in Section B.1.3.1 and outlined in Figure 1, the indications for the majority of patients undergoing alloSCT are malignant disorders such as AML, ALL, MDS/MPN and lymphoma; alloSCT is a potentially curative therapy for some of those diseases (6). Patients undergoing alloSCT are typically hospitalised for 1–1.5 months. There is a high level of psychological distress surrounding alloSCT for both patient and caregiver, with alloSCT recipients requiring a full-time caregiver for the first 100 days post-transplant or longer (41, 42).

After alloSCT, patients will still have an approximately 50% chance of developing aGvHD, which can be a debilitating disease associated with high mortality, significant morbidity, and

compromised quality of life (11). Mortality in aGvHD may occur from the primary malignancy, aGvHD itself or infections resulting from immunosuppressive treatment (13). Non-responders to steroid therapy have very poor survival, with only 25% of patients alive 2 years after diagnosis, decreasing further to 10% at 4 years (13, 14). While 3-year overall survival (OS) rates for aGvHD Grade II have been estimated at 54%, steroid-responsive patients are twice more likely to be alive at 2 years than patients with SR-aGvHD (43, 44).

As previously discussed in Section B.1.3.1, the diagnosis of acute vs chronic GvHD is based on clinical manifestations rather than time elapsed from transplant (36, 37) and symptoms of aGvHD may persist from several months to years after alloSCT (45). In aGvHD, skin is usually the first organ affected, with a characteristic pruritic, maculopapular rash that can disseminate throughout the body surface and be painful. In severe cases, blistering, ulceration and epidermal necrosis may be present (1, 2, 16). The GI tract and the liver are the other two target organs of aGvHD. Both upper and lower GI tract are usually involved, with symptoms ranging from nausea, vomiting and anorexia to diarrhoea and abdominal pain. Involvement of the lower GI tract can be severe, with bloody/voluminous diarrhoea (which may be greater than 10 L per 24 hours) (1, 2). Rectal bleeding usually occurs as a result of mucosal ulceration and carries a poor prognosis (1, 16). Liver involvement usually occurs only if the skin and/or GI tract are involved, and manifests itself as deranged liver function tests (LFT), with elevated bilirubin and alkaline phosphatase levels (2). Staging of liver aGvHD is based on serum bilirubin levels; increased total serum bilirubin level can lead to jaundice (16). Additional clinical signs of liver aGvHD are painful hepatomegaly, dark urine/pale stools and fluid retention (19). As well as disease-related symptoms, patients may experience side effects from corticosteroid treatment for aGvHD, as discussed in Section B.1.3.3.

B.1.3.4.2. Humanistic burden of aGvHD

Whether disease- or treatment-related, the heavy symptom burden experienced by patients with aGvHD following alloSCT significantly affects their health-related quality of life (HRQoL) (11, 17, 18). A Czech study described patient-reported outcomes (PRO) following alloSCT, using the Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire, and found that aGvHD significantly contributed to the deterioration of quality of life (QoL) in terms of physical (p=0.003), emotional (p=0.005) and functional well-being (p=0.003), compared with alloSCT controls (alloSCT recipients without GvHD) (17). A Swedish study investigating the general health and symptom occurrence in alloSCT recipients also found that patients

with aGvHD had significantly poorer general health (as measured by the 36-item Short Form Health Survey [SF-36]) than alloSCT controls (p=0.025) and a significantly higher symptom burden (as measured by the Symptom, Frequency, Intensity, and Distress Questionnaire for Stem Cell Transplantation [SFID-SCT] – p=0.005) (18).

Patients' with SR-aGvHD experience poor QoL, as measured by the EuroQol five-dimension five-level (EQ-5D-5L) questionnaire: data from a cross-sectional survey indicated that SR-aGvHD was associated with worse EQ-5D-5L scores (0.53) than steroid-responsive disease (0.83). Overall, three of the five EQ-5D-5L domains had the greatest impact on scores: 60.9% of patients with aGvHD had problems performing usual activities, 76.6% experienced pain/discomfort, and 64.1% experienced anxiety/depression (46).

B.1.3.4.3. Economic burden

There is a high economic burden associated with aGvHD, particularly with Grade III–IV disease. The direct costs arise from treatment of the disease or of infections related to immunosuppressive therapy and relate primarily to hospitalisation, drug therapy, and radiology (10). A study found that the mean cost of readmission following alloSCT was higher in patients with GvHD (£28,860) than in non-GvHD patients (£13,405; p=0.002), and in patients with Grade III/IV aGvHD (£40,012) compared with those patients with Grade I/II aGvHD (£24,560; p=0.038) (10). The total costs of treatment for patients with Grade III/IV aGvHD (£76,036) were also significantly higher than those for patients with Grade I/II aGvHD (£49,030; p=0.002). Although reports on aGvHD-associated costs in the UK are limited, a retrospective study conducted in Sweden found that one-year costs were significantly higher in patients with Grade III/IV aGvHD than in those without GvHD (p<0.001) (47). Mean one-year costs were approximately €140,000 in a typical alloSCT recipient, compared with approximately €250,000 in a patient with Grade III/IV aGvHD. A retrospective French study found that directs costs were significantly higher for patients with aGvHD then those without (€205,305 vs €174,482, p<0.001; mean follow-up duration: 27.2 months). Additionally, the study reported an average of €10,784 for indirect and non-medical costs incurred by patients with aGvHD, over the entire follow-up period (48).

B.1.3.5. Clinical pathway of care

B.1.3.5.1. Current treatment

Treatment guidelines for aGvHD are available from The European Society for Blood and Marrow Transplantation (EBMT), the British Committee for Standards in Haematology

(BCSH)-BSBMT, the American Society for Transplantation and Cellular Therapy (ASTCT) and the National Comprehensive Cancer Network® (NCCN®) (19, 26, 39, 49). There is also a National Health Service (NHS) Clinical Commissioning Policy for Treatments for Graft versus Host Disease (GvHD) following Haematopoietic Stem Cell Transplantation (12). Although these guidelines are available, there was no consensus among the UK clinical experts contacted as part of this submission on which one is predominantly used (9).

The EBMT guidelines recommend systemic corticosteroid therapy for Grade ≥II aGvHD and the primary use of ruxolitinib for SR-aGvHD (26). The BCSH-BSBMT and the ASTCT guidelines provide similar recommendations in terms of 1L systemic corticosteroid therapy for Grade ≥II aGvHD. The ASTCT guidelines note that the only Food and Drug Administration (FDA)-approved second-line (2L) therapy is ruxolitinib, which is the only Category 1 agent [a] recommended by NCCN® for the treatment of both acute and chronic GvHD (49). The BCSH-BSBMT recommend the following agents for use in 2L treatment: extracorporeal photopheresis (ECP), anti-tumour necrosis factor α antibodies, mammalian target of rapamycin (mTOR) inhibitors, mycophenolate mofetil (MMF), interleukin-2 receptor antibodies (19, 39) (Table 6). Notably, in September 2022, the BSBMTCT released a position statement on the use of ruxolitinib in GvHD (27). In this statement, the BSBMTCT strongly recommend that ruxolitinib should be made available equitably across the UK for patients with SR-GvHD.

Table 6: Recommended 2L treatments for aGvHD

Drug	ASTCT (39)	BCSH-BSBMT (19) / BSBMTCT (27)	EBMT (26)	NCCN® (49)	NHS Clinical Commissio-ning Policy (12)
anti-tumour necrosis factor α antibodies	No	Yes	No	No	No
ECP	No	Yes	No	No	Yes
interleukin-2 receptor antibodies	No	Yes	No	No	No
MMF	No	Yes	No	No	No
mTOR inhibitors	No	Yes	No	No	No
Ruxolitinib	Yes	Yes[†]	Yes	Yes	No

[a] In the NCCN® guidelines, drugs are classed as “Category 1” based upon high-level evidence, and where there is uniform NCCN® consensus that the intervention is appropriate.

† As part of BSBMTCT position statement, September 2022.
Abbreviations: 2L, second-line; aGvHD, acute graft-versus-host-disease; ASTCT, American Society for Transplantation and Cellular Therapy; BCSH, British Committee for Standards in Haematology; BSBMT(CT), British Society of Blood and Marrow Transplantation (and Cellular Therapy); EBMT, European Society for Blood and Marrow Transplantation; ECP, extracorporeal photopheresis; MMF, mycophenolate mofetil; mTOR, mammalian target of rapamycin; NCCN®, National Comprehensive Cancer Network®; NHS, National Health service.

UK clinical experts explained that patients with Grade I aGvHD will most frequently present with skin aGvHD, for which patients will receive topical steroid therapy. Grade II and above aGvHD is typically treated with systemic corticosteroids (between 1.5 – 2 mg/kg/day, depending on severity of symptoms), topical steroids if the patient presents with skin symptoms, and non-absorbable steroids if presenting with GI symptoms. In addition, patients with aGvHD are likely to receive calcineurin inhibitors (CNI) and/or MMF (9).

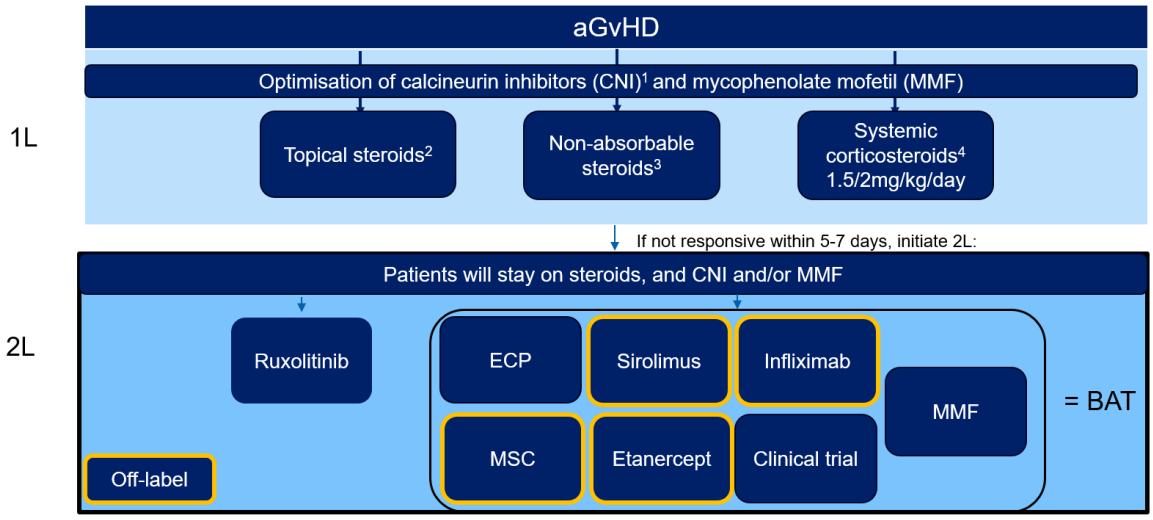
Based on feedback from four UK clinical experts consulted as part of this submission, if a patient does not respond to treatment within 7 days, they are considered steroid-refractory. In the 2L setting, patients with SR-aGvHD are likely to continue CNI and/or MMF in addition to systemic steroids they have been receiving as first-line therapy, but 2L treatment options are limited. The most common 2L treatment is ECP, assuming the patient is haematologically stable, has good venous access, and has access to a site that offers this treatment. If ECP is not an option, UK clinical experts will use off-label therapies such as etanercept, infliximab, mesenchymal stromal cells (MSC), and sirolimus (9). These are used to varying extents in UK clinical practice. It is worth noting that, while ruxolitinib is not routinely commissioned, some centres will use their own budgets to provide ruxolitinib to GvHD patients.

B.1.3.5.1.1 Positioning of ruxolitinib

Ruxolitinib is indicated for the treatment of SR-aGvHD in patients 12 years and older who have inadequate response to corticosteroids, which is the proposed positioning of ruxolitinib in this submission. This aligns with the Phase 3 randomised controlled trial (RCT) REACH2 (50, 51), EBMT guidelines recommending ruxolitinib as the primary treatment for SR-aGvHD (26), ruxolitinib use as per the Coronavirus disease 2019 (COVID-19) NHS England (NHSE) Rapid Commissioning Policy (30), and UK clinical expert opinion (9). Ruxolitinib is therefore expected to be used in the same position in the treatment pathway as ECP, combination therapy with mTOR inhibitors (for example, sirolimus) and/or MMF, as well as infliximab, etanercept, and MSCs (Figure 3)

The current treatment pathway for patients aged 12 years and above with SR-aGvHD in the UK together with the potential positioning of ruxolitinib is summarised in Figure 3, based on feedback from UK clinical experts who were consulted as part of this submission (9).

Figure 3: Current treatment pathway for aGvHD with proposed positioning of ruxolitinib



[1]Tacrolimus or cyclosporine. [2]Hydrocortisone, eumovate, betnovate, dermovate. [3]Budesonide or beclomethasone, to reduce dose of systemic steroids. [4]Methyl/prednisolone.
Boxes with a yellow outline represent treatments currently used off-label in the UK as informed by clinical experts.
Abbreviations: 1L, first line; 2L, second line; aGvHD, acute graft-versus-host-disease; BAT, best available therapy; CNI, calcineurin inhibitor; ECP, extracorporeal photopheresis; MMF, mycophenolate mofetil; MSC, mesenchymal stromal cells.

B.1.3.5.2. Limitations of current treatments and unmet need

Despite their use, there is limited clinical evidence available for the majority of the treatments currently used in UK clinical practice for patients with SR-aGvHD. There was a consensus among all four UK clinicians consulted that the currently available treatment options are ineffective and lead to major side effects, and that without access to ruxolitinib, a significant unmet need remains in this population (9).

Currently-used therapies have only been evaluated in small, retrospective and non-comparative trials, and response to treatment and long-term survival rates have been low and/or highly variable across studies (20-25). For example, a study of MMF in SR-aGvHD (n=27) found that only 26% of patients had a complete response (CR), with 40% alive at 3 years (52). While the overall response rate (ORR) observed with anti-thymocyte globulin (ATG) can be up to 43%, this does not translate into long-term survival as OS can be as low as 5.5 months (53), with high mortality rates due to infection (9, 54). Additionally, some of these therapies inadequately address the need to reduce corticosteroid use: in a study of

sirolimus in SR-aGvHD, only 17% of patients discontinued steroid therapy (55). Furthermore, the most commonly used second-line treatment, ECP, is inconvenient to administer and expensive (56). The NHS Clinical Commissioning Policy for Treatments for Graft versus Host Disease (GvHD) following Haematopoietic Stem Cell Transplantation has concluded that there is enough evidence to support a proposal for the routine commissioning of ECP for the 2L treatment of aGvHD in patients who are steroid-dependent, or who are unsuitable for, or show incomplete response to, 1L treatment following alloSCT (12); however, ECP is only available in five Therapeutic Apheresis Services (TAS) units (57) across England and Wales, and a limited number of hospital trusts provide ECP services independently (56), which creates inequity of access to treatment, as discussed in Section B.1.4. As a result, patients may have to travel further than to their usual care centre and if using public transport, may increase their risk of contracting an infection, which could be severe due to their immunocompromised state. There is also a risk of device-related infection with ECP, as it has to be administered via a central line, and UK clinicians have reported high rates of line infection, leading to prolonged admissions with neutropenic sepsis (9).

Additionally, some patients are too unwell to travel and will not be able to access ECP treatment at all (12); eligibility for ECP also depends on patients having good venous access and being haematologically stable, and so not all patients are able to receive this treatment option (9). For those patients who are able to travel and able to receive ECP, the treatment schedule for aGvHD can be burdensome: the UK Photopheresis Society recommends a schedule consisting of three sessions in Week 1, two sessions per week in Weeks 2–12, and two sessions per four weeks thereafter, until clinical improvement (58). In UK practice, clinicians have reported a schedule of 12 sessions over a 4–6 week period, followed by one session a week, then one session every 2 weeks, with treatment ranging on average from 6 to 12 months, although some patients may require treatment for as long as two years (9). Although the ECP schedules may vary, they are all extensive and considerably time-consuming.

As discussed in Section B.1.3.4.1, it is well documented that systemic steroid use is associated with toxicity and major adverse events (AE) (39, 40). Feedback from UK clinical experts has confirmed this, and that the lack of alternative, effective therapies to treat aGvHD leads patients back to steroids in later lines of treatment, despite toxicity concerns (9). Notably, there is evidence to support that current treatments such as sirolimus are associated with an inadequate reduction of steroid usage (55).

Patients with SR-aGvHD have a high unmet need for a new effective, well-tolerated, and convenient treatment option for aGvHD, which would:

- Significantly improve response rates and HRQoL
- Reduce the need for corticosteroid treatment, thereby reducing the incidence of corticosteroid-related AEs
- Have a favourable safety profile
- Have been rigorously evaluated in randomised clinical trials
- Be convenient to administer (e.g. oral).

B.1.4. Equality considerations

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 (59). Mismatched HLA donor grafts can contribute to a higher incidence of GvHD in transplant recipients (60), therefore, certain ethnic groups may be more likely to develop aGvHD than others.

The BSBMTCT position statement on the use of ruxolitinib in GvHD reports that, following the termination of the COVID-19 NHSE Rapid Commissioning Policy for ruxolitinib in GvHD, ruxolitinib approval is dependent on either individual funding requests or local approval by individual trusts (27). This is variable and does not guarantee equitable access to ruxolitinib for patients in England. Additionally, in Wales and Scotland, access to ruxolitinib for GvHD continues to be available via local commissioning policies. This creates inequity of access across the UK.

UK clinical experts have confirmed that ECP is the preferred 2L treatment in patients with SR-aGvHD. As described in Section B.1.3.5.2, access to ECP services in England is limited to five TAS centres and a few hospital trusts providing ECP services independently (12, 57), which creates inequity of access to treatment across England. Patients in lower socioeconomic groups may not be able to afford to travel to those centres, even more so as a typical course of treatment may last up to 12 weeks, involving weekly sessions taking place on two consecutive days (56, 58). Those same patients may also have to decline ECP

if they fall outside of the travel distance requirements that would grant them free accommodation between the two therapy days (56).

B.2. Clinical effectiveness

The efficacy and safety of ruxolitinib for the treatment of patients aged 12 years or older with steroid-refractory acute graft-versus-host-disease (SR-aGvHD) following allogeneic stem cell transplant (alloSCT) have been assessed in one pivotal Phase 3 randomised controlled trial (RCT), and one supporting Phase 2 trial.

REACH2, a multicentre, randomised, open-label Phase 3 trial (N=309)

Treatment with ruxolitinib demonstrated a robust clinical benefit and maintained quality of life (QoL), with statistically significant improvements in overall response rate (ORR) and failure-free survival (FFS) vs best available therapy (BAT).

- ORR was significantly higher in the ruxolitinib arm than in the BAT arm: ORR at Day 28 was 62.3% vs 39.4% (odds ratio 2.64; 95% confidence interval [CI]: 1.65, 4.22; p<0.0001)
- FFS was significantly longer with ruxolitinib than with BAT: median FFS was 4.86 months vs 1.02 months, HR: 0.51 (95% CI: 0.39, 0.66; p<0.0001)
- REACH2 showed [redacted] for patients receiving ruxolitinib than those receiving BAT.

The majority of patients treated with ruxolitinib were able to taper off or reduce their corticosteroid usage.

- At end of treatment (EOT), more patients in the ruxolitinib arm (43.5%; 95% CI: 35.5, 51.7) had completely tapered off corticosteroids than in the BAT arm (31.6%; 95% CI: 24.4, 39.6) with odds ratio of 1.67 (95% CI: 1.05, 2.65). The dose reduction achieved at EOT was [redacted] in patients in the ruxolitinib arm than in the BAT arm [redacted]% vs [redacted]%).

REACH1, an open-label, single-cohort phase II trial (N=71)

- The study achieved the predetermined threshold for a positive study outcome (lower limit of the 95% CI for Day 28 ORR ≥ 40%), with ORR at day 28 of 56.3% (95% CI: 44.0, 68.1)
- The best ORR was 76.1% (95% CI: 64.5, 85.4)
- Responses were rapid and durable. The majority of patients (62.0%) achieved their first response within the first 14 days of treatment, with a median time to first response of 8 days; all first responses were achieved before Day 56.

Generally, ruxolitinib was well-tolerated in patients with SR-aGvHD. The addition of ruxolitinib to corticosteroid-based treatment for SR-aGvHD did not result in unexpected toxicities or exacerbation of known toxicities related to high-dose corticosteroids or aGvHD.

- In REACH2, the proportion of patients experiencing at least one AE was similar between the ruxolitinib arm and the BAT arm (99.3% vs 98.7%)
- In REACH2 and REACH1, cytopenias were more frequently reported in the ruxolitinib arm than in the BAT arm, however, this is in keeping with the known pathology of post-alloSCT GvHD and the known safety profile of ruxolitinib; those cytopenias were generally reversible upon discontinuation of ruxolitinib.

B.2.1. Identification and selection of evidence

A systematic literature review (SLR) was conducted to identify all relevant clinical evidence on the efficacy and safety of ruxolitinib and relevant comparators for the treatment of patients aged ≥12 years with steroid-refractory aGvHD or cGvHD. A detailed description of the SLR methodology and search strategies is presented in Appendix D. The SLR comprised a de novo SLR performed in November 2019, a first SLR update conducted in September 2021, and a second SLR update performed in January 2024. Although the literature was reviewed for relevant publications on aGvHD or cGvHD, only publications reporting data on aGvHD are presented here, to align with the current decision problem.

Overall, a total of 211 publications were included (a list of all included publications is provided in Appendix D). Of these, 117 publications were relevant to the current decision problem, comprising 101 publications reporting on aGvHD patients alone, and 16 publications reporting separate data for patients with aGvHD and patients with cGvHD. A further 94 publications reported on cGvHD patients alone, which are not relevant to the current decision problem. The 117 relevant publications reported on 104 unique clinical studies, of which 25 studies evaluated ruxolitinib for the treatment of SR-aGvHD, comprising:

- A Phase 3 RCT of ruxolitinib vs best available therapy (BAT; REACH2, NCT02913261, reported across 8 publications) (51)
- A Phase 2 single-arm trial of ruxolitinib (REACH1; NCT02953678, 3 publications) (61)
- A Phase 2 single-arm trial of ruxolitinib (NCT02997280; 1 publication) (62)
- A Phase 2 single-arm trial of ruxolitinib + etanercept combination therapy (ChiCTR1900024408; 1 publication) (63)
- 21 observational studies involving ruxolitinib (22 publications).

Further information on the REACH2 and REACH1 trials are provided in the sections that follow. REACH2 was the pivotal Phase 3 trial of ruxolitinib vs BAT (51), while REACH1 further supports the efficacy and safety profile of ruxolitinib (61). NCT02997280 was deprioritised because it only included 32 patients with aGvHD and recruited patients in

Russia alone (62). Meanwhile, ChiCTR1900024408 was deprioritised because it only included 64 patients with aGvHD, recruited patients in China alone, and focused specifically on the combination of ruxolitinib and etanercept (63).

B.2.2. List of relevant clinical effectiveness evidence

The primary sources of clinical effectiveness evidence for ruxolitinib are:

- The Phase 3 RCT REACH2, in patients ≥12 years of age with SR-aGvHD after alloSCT (Grade II-IV) (50, 51)
- The Phase 2 REACH1, in patients ≥12 years of age with SR-aGvHD after alloSCT (Grade II-IV) (61, 64)

An overview of the two ruxolitinib in SR-aGvHD trials REACH2 and REACH1 is provided in Table 7. Data from REACH1 were not used in the economic model but are included in the submission as supporting evidence for ruxolitinib in SR-aGvHD.

Table 7: Clinical effectiveness evidence

Study	REACH2 (NCT02913261)	REACH1 (NCT02953678)
Study design	Phase 3, randomised, open-label, multicentre study	Phase 2, single cohort, open-label, multicentre, prospective study
Population	Patients (≥12 years of age) with SR-aGvHD (Grade II-IV) after alloSCT	Patients (≥12 years of age) with SR-aGvHD (Grade II-IV) after alloSCT
Intervention(s)	Ruxolitinib	Ruxolitinib
Comparator(s)	BAT (ECP, MMF, etanercept, ATG, infliximab, MSCs, low-dose MTX, sirolimus, everolimus)	None
Indicate if study supports application for marketing authorisation	Yes	Yes
Indicate if study used in the economic model	Yes	No
Rationale if study not used in model	N/A	REACH1 was a Phase 2 single cohort study and therefore did not provide results vs a relevant comparator
Reported outcomes specified in the decision problem†	• Response to treatment (including complete response and overall response)	• Response to treatment (including complete response and overall response)

	• **OS** • **FFS (defined as the time from the date of randomisation to date of haematological disease relapse / progression, NRM or addition of new systemic aGvHD treatment; the competing risk was cGvHD)** • **Adverse effects of treatment** • **Health-related quality of life**	• OS • FFS (defined as the time from first dose of ruxolitinib to the earliest date that a patient died, had a relapse/progression of the underlying malignancy, required additional therapy for aGvHD, or demonstrated signs or symptoms of cGvHD) • Adverse effects of treatment • Health-related quality of life
All other reported outcomes	• EFS • Incidence of cGvHD • To describe cumulative steroid dosing until Day 56, and until EOT • Pharmacokinetics of ruxolitinib	• Pharmacokinetics of ruxolitinib

† Outcomes **in bold** are those used in model
Abbreviations: alloSCT, allogeneic stem cell transplant; ATG, anti-thymocyte globulin; BAT, best available therapy; cGvHD, chronic graft-versus-host-disease; ECP, extracorporeal photopheresis; EFS, event-free survival; EOT, end of treatment; FFS, failure-free survival; MMF, mycophenolate mofetil; MSC, mesenchymal stromal cell; MTX, methotrexate; NRM, non-relapse mortality; OS, overall survival; SR-aGvHD, steroid-refractory acute graft-versus-host-disease.

B.2.2.1. Data presented in the submission

The key REACH2 data considered in this submission are from two data cut-off (DCO) dates. Response rates data are from the primary analysis (DCO: 25th July 2019), and data from all other outcomes are from the final analysis (cumulative data until end of study [EOS – up to 24 months after randomisation]). Notably, although data were available for up to 24 months after randomisation, three patients had longer follow-up data (up to 36 months) available for OS analysis (Section B.2.6.1.2.4), failure-free survival (FFS) analysis (Section B.2.6.1.2.5) and event-free survival (EFS) analysis (Section B.2.6.1.2.10).

Data from REACH1 come from one DCO only (5th July 2019).

The cost-effectiveness analysis is based on the completed REACH2 trial (23rd April 2021).

B.2.2.2. Clinical validation

As part of this submission, UK clinical experts were consulted in order to gain feedback on treatment options available to patients with SR-aGvHD, the methodology and outcomes of the REACH trials and the proposed economic model. Feedback was gained during the following:

- Individual validation calls with four UK clinicians, conducted in February and March 2024 (9)

- An advisory board with four UK clinicians and one health economist, conducted on 15th May 2024 (65). An additional clinical expert, who was not able to make the advisory board due to unavailability, was consulted on Thursday 23rd May to gather their input.

Further detail regarding clinical validation can be found in Section B.3.13, the individual validation calls consolidated report (9) and the advisory board report (65)

B.2.3. Summary of methodology of the relevant clinical effectiveness evidence

A summary of the study designs and methodology of REACH2 and REACH1 is presented in Table 8. A list of all inclusion and exclusion criteria is presented in Appendix M.

Table 8: Comparative summary of trial methodology

	REACH2	REACH1
Location	105 treatment centres across 22 countries	26 treatment centres across the US
Trial design	Multicentre, randomised, open-label, global Phase 3 trial comparing the efficacy and safety of ruxolitinib with the investigator's choice of therapy from a list of nine commonly used options (control) in patients 12 years of age or older who had glucocorticoid-refractory aGvHD after alloSCT	Multicentre, single-cohort, open-label, Phase 2 study of ruxolitinib in combination with corticosteroids in patients (≥12 years old) with Grades II to IV SR-aGvHD
Key inclusion criteria for patients	• Aged ≥12 years old at the time of informed consent • Had undergone alloSCT from any donor source using bone marrow, PBSCs, or cord blood • Clinically diagnosed Grade II to IV aGvHD as per MAGIC guidelines (66) • Evident myeloid and platelet engraftment (confirmed within 48h prior to study treatment start): ANC >1000/mm^3 and platelets ≥20,000/mm^3. Use of growth factor supplementation and transfusion support was allowed.	• Aged ≥12 years old at the time of informed consent • Had undergone first alloSCT from any donor source using bone marrow, PBSCs, or cord blood • Clinically suspected Grade II–IV aGvHD as per MAGIC guidelines (66) • Evidence of myeloid engraftment (e.g., ANC ≥0.5 × 10^9/L for 3 consecutive days if ablative therapy was previously used). Use of growth factor supplementation was allowed.
Key exclusion criteria for patients	• Failed prior alloSCT within the past 6 months • Received more than one systemic treatment for SR-aGvHD • Clinical presentation resembling de novo cGvHD or GvHD overlap syndrome • Presented with active uncontrolled infection • Presented with relapsed primary malignancy, or patients who were treated for relapse after the alloSCT was performed, or who may require rapid immune suppression withdrawal as pre-emergent treatment of early malignancy relapse. A full list of the inclusion and exclusion criteria is reported in the REACH2 CSR and is also presented in Appendix M	• Received more than one alloSCT • Received more than one systemic treatment in addition to corticosteroids for aGvHD • Presence of GvHD overlap syndrome • Presence of an active uncontrolled infection • Evidence of relapsed primary disease or patients who have been treated for relapse after the alloSCT was performed A full list of the inclusion and exclusion criteria is reported in the REACH1 CSR and is also presented in Appendix M
Method of study drug administration	• 309 patients randomised 1:1 to receive either ruxolitinib (n=154) or BAT (n=155)	• Ruxolitinib 5 mg BID (oral tablets) • Dose could be increased to 10 mg BID if haematological parameters were stable and no treatment-related toxicity

	REACH2	REACH1
	Ruxolitinib arm • Ruxolitinib 10 mg BID (as two 5 mg oral tablets) • Within the first 28 days, patients with aGvHD disease progression, or mixed response, or no response, could select new systemic treatment per investigator choice. This was considered a treatment failure, and the patient discontinued study treatment. • Ruxolitinib dose reductions or modifications were allowed for safety reasons. • Patients responding to treatment were tapered off ruxolitinib as needed, starting no earlier than Day 56. The dose tapering strategy was based on evaluation of the condition of the patient, current dosing regimen and the clinical judgment of the investigator **BAT arm** • Patients received BAT based on the investigator's best judgment • A new immunosuppressive agent could be added to ruxolitinib or BAT treatment regimen if the patient met the criteria for disease progression, no response, or mixed response, or aGvHD flare	was observed after the first 3 days of treatment • After Day 180, ruxolitinib could be tapered if the patient had achieved a CR or VGPR and had discontinued corticosteroids for at least 8 weeks. • Dose reductions or modifications of ruxolitinib are permitted based on AEs, clinical evaluation, and laboratory assessments
Permitted and disallowed concomitant medication	**The following medications were permitted:** Supportive treatments for management of patients with SR-aGvHD**,** systemic corticosteroids, CNI, topical corticosteroid therapy, aGvHD prophylaxis medications, antibiotics, anti-infectives, immunisations, additional supportive care measures. **The following medications were disallowed:** Aspirin, NSAIDs or related medications, concomitant use of another JAK inhibitor, investigational medication, chemotherapeutic agents and/or non-schedules DLI, pre-emergent intervention related to graft failure or haematological disease relapse/progression, Fluconazole at daily doses higher than 200 mg.	**The following medications were permitted:** GvHD prophylaxis medications, additional supportive care measures, biologic agents for treatment of non-cancer indications. **The following medications were disallowed:** concurrent anticancer therapy, secondary GvHD therapy due to insufficient response/progression on study treatment, concomitant use of another JAK inhibitor, investigational medication unless approved by medical monitor.
Primary outcomes	ORR at Day 28 after randomisation, defined as the proportion of patients in each arm demonstrating a CR or PR without	ORR at Day 28, defined as the proportion of patients demonstrating a response (CR, VGPR, or PR) as per the

	REACH2	REACH1
	requirement for additional systemic therapies for an earlier progression, mixed response or non-response. Scoring of response was relative to the organ stage at the time of randomisation	CIBMTR modifications to the IBMTR response index at the Day 28 response assessment (± 2 days) and before the start of new anti-aGvHD therapy, if applicable
Secondary outcomes	• Durable ORR at Day 56 • ORR (CR+PR) at Day 14 • DOR was assessed for responders only and was defined as the time from first response until aGvHD progression or the date of additional systemic therapies for aGvHD. Onset of chronic GvHD, or death without prior observation of aGvHD progression are considered as competing risks • Weekly cumulative steroid dose for each patient up to Day 56 • OS, defined as the time from the date of randomisation to the date of death due to any cause • EFS, defined as the time from the date of randomisation to the date of haematological disease relapse / progression, graft failure, or death due to any cause • FFS (defined as the time from the date of randomisation to date of haematological disease relapse/progression, NRM, or addition of new systemic aGvHD treatment) • NRM, defined as the time from date of randomisation to date of death not preceded by haematological disease relapse/progression • Malignancy relapse / progression, defined as the time from date of randomisation to haematological malignancy relapse/progression • Incidence of cGvHD, defined as the diagnosis of any cGvHD, including mild, moderate or severe • BOR: proportion of patients who achieved OR (CR+PR) at any time point up to and including Day 28 and before the start of any additional systemic therapy for a GvHD • PK parameters of ruxolitinib after a single dose and at steady state: C_{max}, AUC_{last}, and AUC_{inf}, C_{trough}, R_{acc} and AUC_{tau}; other PK parameters are CL/F, Vz/F, T_{max} and T1/2	• Six-month DOR (patients still on study completed the Day 180 visit) • ORR, defined as the proportion of patients demonstrating a CR, VGPR, or PR at Days 14, 56, and 100 • 3-month DOR, defined as the time from first response until GvHD progression or death, when all patients who were still on study complete the Day 84 visit) • NRM (defined as the proportion of patients who died due to causes other than malignancy relapse at Months 6, 9, 12, and 24) • Relapse rate, defined as the proportion of patients whose underlying malignancy relapsed • Relapse-related mortality rate, defined as the proportion of patients whose malignancy relapsed and had a fatal outcome • FFS (defined as the time from first dose of ruxolitinib to the earliest date that a patient died, had a relapse/progression of the underlying malignancy, required additional therapy for aGvHD, or demonstrated signs or symptoms of cGvHD) • OS, defined as the time from study enrolment (first dose of ruxolitinib treatment) to death due to any cause • AEs and serious AEs: summaries of clinical safety data (e.g. AEs, infections) were tabulated and listed • PK of ruxolitinib when administered in combination with corticosteroids: C_{max}, C_{min}, T_{max}, AUC, and CL/F.

	REACH2	REACH1
	• Changes in FACT-BMT and in in EQ-5D from baseline to each visit where measured • Safety and tolerability including myelosuppression, infections, and bleeding were assessed by monitoring the frequency, duration, and severity of AEs	
Pre-planned subgroup analyses of primary endpoint	**Subgroups for the primary efficacy endpoint analysis:** • Age group • Gender • Race • Region • Acute GvHD grade • Source of grafts • Criteria for SR-aGvHD • Prior aGvHD • Conditioning regimen • Stem cell type • Donor HLA status • Donor gender match • Donor CMV status • Donor source/HLA match status • aGvHD organ involvement at randomisation	**Subgroups for the primary efficacy endpoint analysis:** • Baseline SR-aGvHD grade • Baseline steroid-refractory status • Use of immunosuppressant medication and CNIs • Average ruxolitinib dose from Day1 to Day 28 • Age group (<65, ≥65 years) • Gender • Race • Baseline organ involvement.

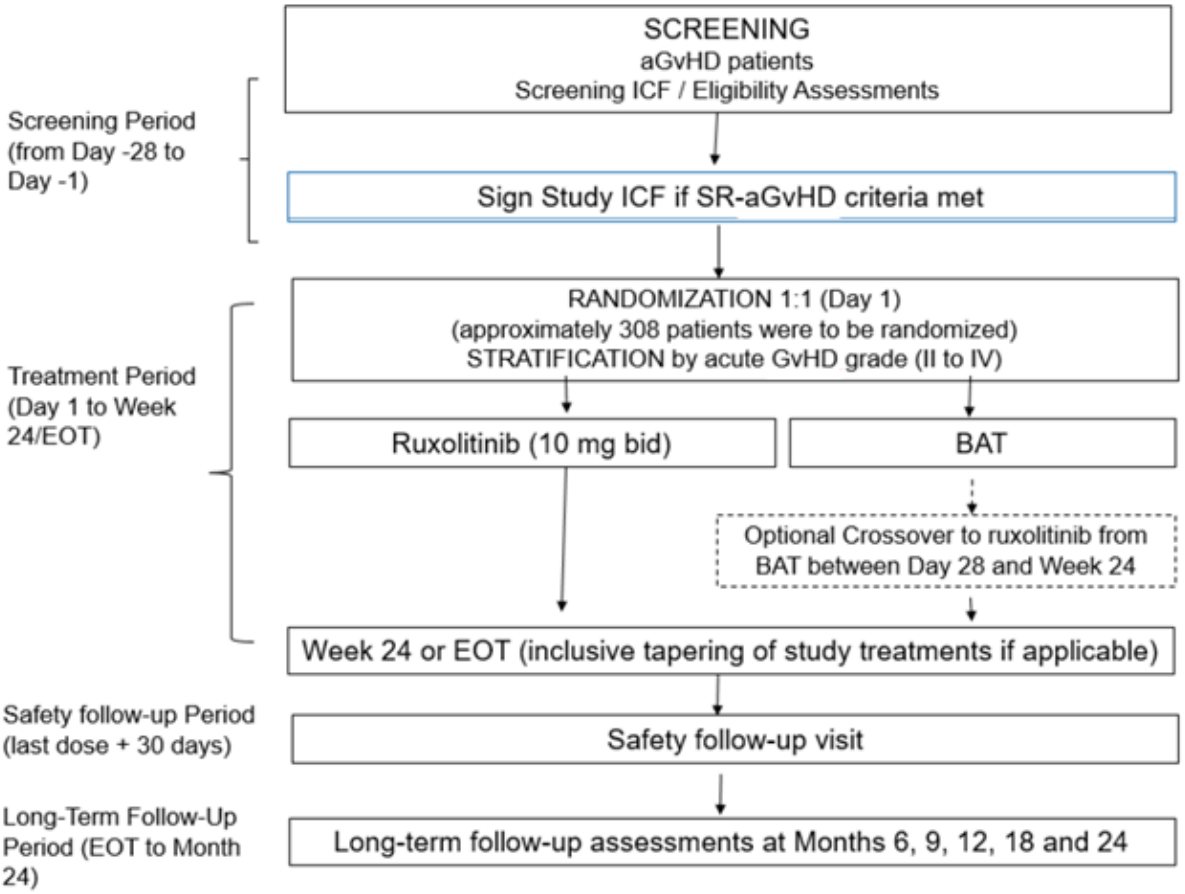
Source: REACH2 final analysis CSR (50), REACH2 SAP (67), REACH1 final analysis CSR (64).
Abbreviations: AE, adverse event; aGvHD, acute graft-versus-host-disease; alloSCT, allogeneic stem cell transplant; ANC, absolute neutrophil count; AUC, area under the curve; AUC_{inf}, AUC from time zero to infinity; AUClast, AUC from time zero to the last measurable concentration sampling time; AUC_{tau}, AUC calculated to the end of a dosing interval (12 hr) at steady-state; BAT, best available therapy; BID, twice a day; BK virus, human polyomavirus 1; cGvHD, chronic graft-versus-host-disease; CIBMTR, Center for International Blood and Marrow Transplant Research; CL/F, apparent clearance of study drug from plasma; C_{max}, maximum observed plasma drug concentration; C_{min}, minimum observed plasma drug concentration; CMV, cytomegalovirus; CNI, calcineurin inhibitor; CR, complete response; CSR, clinical study report; C_{trough}, observed plasma drug concentration obtained prior to administration of the next dose; CYP2C9, cytochrome P450, family 2, subfamily C, member 9; CYP3A, cytochrome P450, family 3, subfamily A; DLI, donor lymphocyte infusion; EBV, Epstein-Barr virus; ECOG, Eastern Cooperative Oncology Group; F, female; FFS, failure-free survival; GI, gastrointestinal tract; HBV, hepatitis B virus; HCV, hepatitis B virus; HHV-6, human herpes virus 6; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; IBMTR, International Blood and Marrow Transplant Registry; JAK, Janus kinase; LMWH, low molecular weight heparin; M, male; MAGIC, Mount Sinai acute GvHD International Consortium; MRU, medical resource utilisation; NIH, National Institutes of Health; NRM, non-relapse mortality; NSAID, non-steroidal anti-inflammatory drug; PBSC, peripheral blood stem cell; PK, pharmacokinetics; PR, partial response; R_{acc}, accumulation ratio; ROW, rest of world; SAP, statistical analysis plan; SR-aGvHD, steroid-refractory acute graft-versus-host-disease; SR-cGvHD, steroid-refractory chronic graft-versus-host-disease; T1/2, elimination half-life; T_{max}, time of maximum plasma drug concentration; US, United States; VGPR, very good partial response; Vz/F, apparent volume of distribution during terminal phase.

B.2.3.1. Study design

REACH2

REACH2 was a Phase 3, randomised, open-label, multicentre study of ruxolitinib vs BAT in patients with SR-aGvHD after alloSCT. In total, 309 patients were randomised 1:1 to receive either ruxolitinib (n=154) or BAT (n=155). The BAT in REACH2 was identified by the investigator prior to patient randomisation among the following treatments currently used in this setting: ATG, ECP, MSCs, low-dose methotrexate (MTX), MMF, mTOR inhibitors (everolimus or sirolimus), etanercept, or infliximab. The most common initial BAT, administered to 27.3% of patients was ECP, followed by MMF (16.7%), etanercept (14.7 %), ATG (13.3%), infliximab (11.3%) and MSCs (10.0%). The study design of REACH2 is summarised in Figure 4.

Figure 4: Study design of REACH2



Source: REACH2 final analysis CSR (50).
Abbreviations: aGvHD, acute graft-versus-host-disease; BAT, best available treatment; bid, twice a day; CSR, clinical study report; EOT, end of treatment; ICF, informed consent form; SR-aGvHD, steroid-refractory acute graft-versus-host-disease.

The study comprised four periods:

- **Screening period** (Day –28 to Day –1)

- **Treatment Period** (Day 1 to Week 24 / end of treatment [EOT]): study treatment began on Day 1 (no later than 72 hours after randomisation) followed by regular visits for assessments of efficacy and safety. Study treatment was administered until the patient met any of the criteria for discontinuation of study treatment or, in responders. until the dosing schedule for ruxolitinib or BAT was completed. Assessments were also performed within 7 days from last dose, either at a scheduled or unscheduled visit. Responders could be tapered off during the treatment period, first for corticosteroids, followed by CNI and ruxolitinib. A slow tapering could be performed for ruxolitinib at investigator's discretion rather than an abrupt cessation, as the latter could result in an aGvHD flare. The EOT visit occurred when the patient completed the study treatment period or earlier if the patient met any of the criteria for discontinuation of study treatment.

    - During the treatment period, patients randomised to BAT were eligible to cross over to ruxolitinib between Day 28 and Week 24 if they failed to meet the primary endpoint response definition at Day 28 or lost the response thereafter and met criteria for progression, mixed response, or no response, necessitating new additional systemic immunosuppressive treatment for aGvHD and did not have signs/symptoms of cGvHD (overlap syndrome, progressive, or de novo cGvHD). Patients who crossed over to ruxolitinib were followed until completion of treatment with ruxolitinib and received the same treatment and tapering schedule as patients randomised to ruxolitinib treatment. Crossover EOT visits and assessments were the same as for EOT except that the procedures started at Crossover Week 24.

- **Safety follow-up** (last dose +30 days): a 30-day safety follow-up visit was performed for all patients after the last dose of ruxolitinib (administered during treatment period or after crossover) or BAT.

- **Long-term follow-up** (From EOT to Month 24): all patients were followed up for long-term observation up to 24 months from randomisation. During this period, long-term data was collected: survival, any relapse/progression of the underlying haematological disease for which the alloSCT procedure was performed, NRM, any occurrence of graft failure, EFS, any occurrence of cGvHD, and occurrence of any

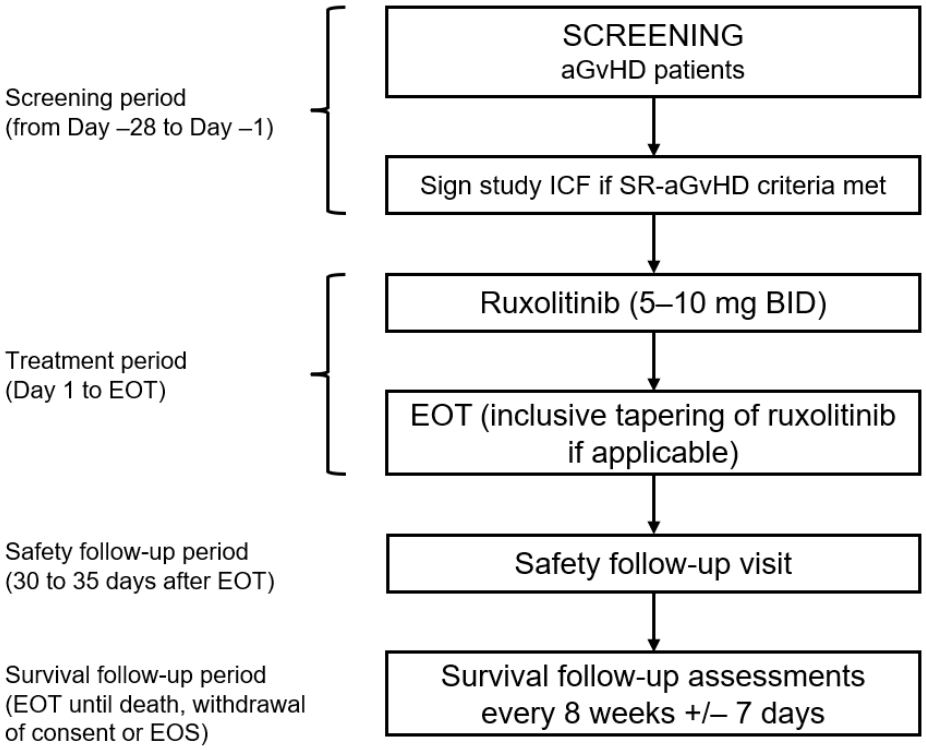
second primary malignancies. Visits for these assessments occurred after EOT or crossover EOT, at 6, 9, 12, 18, and 24 months from randomisation (Day 1), as applicable, after completion of the treatment period.

REACH1

REACH1 was a Phase 2, single-cohort, open-label, multicentre study of ruxolitinib in combination with corticosteroids in patients with Grades II to IV SR-aGvHD after alloSCT. Seventy-one patients began treatment with ruxolitinib at 5 mg twice a day (BID); if haematological parameters were stable and no treatment-related toxicity was observed after the first 3 days of treatment, the dose could be increased to 10 mg BID.

Study participation was expected to average 12 months: 28 days for screening, approximately 9 months for treatment (length of time estimated for patients to be deriving benefit), 30 to 35 days after treatment ended for safety follow-up, and a survival follow-up period lasting until death, withdrawal of consent, or the end of the study, whichever occurred first. The study design of REACH1 is summarised in Figure 5.

Figure 5: Study design of REACH1



Abbreviations: aGvHD, acute graft-versus-host-disease; BID, twice a day; EOT, end of treatment; EOS, end of study; ICF, informed consent form; SR-aGvHD, steroid-refractory acute graft-versus-host-disease.

B.2.3.2. Randomisation

In REACH2, patients were randomised 1:1 to receive either ruxolitinib or BAT. Patients were stratified by aGvHD grade (Grade II vs III vs IV).

A patient randomisation list was produced by the Interactive Response Technology (IRT) provider using a validated system that automated the random assignment of patient numbers to randomisation numbers. Prior to dosing, all patients who met the eligibility criteria were randomised via IRT to one of the treatment arms. When the investigator or their delegate confirmed that the patient fulfilled all the inclusion/exclusion criteria, the IRT assigned a randomisation number to the patient. This randomisation number linked the patient to a treatment arm and specified a unique medication number for the first package of study treatment to be dispensed to the patient on the ruxolitinib arm.

REACH1 was a single-arm study.

B.2.3.3. Blinding

Not applicable, as REACH2 and REACH1 were open-label trials and therefore, no treatment blinding occurred.

B.2.3.4. Eligibility criteria

Key eligibility criteria for REACH2 and REACH1 are provided in Table 8. Full inclusion and exclusion criteria are provided in Appendix M.

B.2.3.5. Tapering guidelines

As discussed in Section B.2.3.1, patients in REACH2 and REACH1 who responded to treatment (CR or partial response [PR]) were tapered off ruxolitinib as needed.

REACH2

Patients responding to treatment (whether after randomisation or after Crossover) were tapered off ruxolitinib as needed, starting no earlier than Day 56. The dose tapering strategy was based on evaluation of the condition of the patient, current dosing regimen and the clinical judgment of the Investigator:

- If a taper of ruxolitinib was indicated, it had to be completed by no later than Week 24 (or Crossover Week 24) unless prolonged tapering was required due to an aGvHD flare or other safety concerns. In such cases, the taper of ruxolitinib was initiated no

later than Week 24 (or Crossover Week 24) and completed by no later than the patient's EOS (up to approximately 2 years from randomisation)

- Should a tapering strategy not be in the best interest of the patient, or if the taper was completed prior to Week 24 (or Crossover Week 24, as applicable), the patient had to follow the assigned Visit Evaluation Schedule including all safety and efficacy assessments, until Week 24 (or Crossover Week 24, as applicable).

Tapering of immunosuppression therapy was performed in two steps:

1. Taper of corticosteroids: initiated not earlier than Day 7, and performed as per institutional guidelines

2. Taper of CNI and/or ruxolitinib would be initiated once the patient stopped corticosteroids as follows: CNI taper was performed as per institutional guidelines; ruxolitinib taper was initiated after Day 56, and performed based on the condition of the patient, current dosing regimen and the clinical judgement of the Investigator.

The taper of corticosteroids, CNIs, and ruxolitinib had to be completed by Week 96 (unless prolonged tapering of ruxolitinib was required due to an aGvHD flare, in which case taper had to be completed by no later than patient's EOS).

REACH1

After Day 180, ruxolitinib could be tapered provided the participant had achieved a CR or very good partial response (VGPR) and had discontinued corticosteroids for at least 8 weeks. Corticosteroids were tapered as per institutional guidelines at a rate commensurate with resolution of GvHD symptoms.

B.2.3.6. Patient disposition

REACH2

A total of 309 patients were included in the full analysis set (FAS), 154 in the ruxolitinib arm and 155 in the BAT arm. A total of 55 patients (17.8%) across both treatment arms completed the treatment period. More patients in the ruxolitinib arm (35; 22.7%) completed the treatment period than in the BAT arm (20; 12.9%). A total of 119 (77.3%) patients in the ruxolitinib arm and 135 (87.1%) patients in the BAT arm discontinued treatment during the randomised treatment period. The most common reasons for discontinuation (ruxolitinib vs

BAT arm) were lack of efficacy (20.8% vs 44.5%), death (16.2% vs 14.2%) and AEs (17.5% vs 3.2%).

Following discontinuation of BAT, 49/155 patients (31.6%) crossed over to ruxolitinib treatment, of whom 29 (59.2%) entered the long-term follow-up phase. The median (range) time to crossover was [redacted]. [redacted] of these 49 patients had completed the crossover treatment period with ruxolitinib. [redacted] patients discontinued crossover treatment period, the most common reason being [redacted]

A total of 102 patients (66.2%) in the ruxolitinib arm entered the long-term follow-up. In the BAT arm, 80 patients (51.6%) entered the long-term follow-up (51 after the randomised treatment period and 29 after completing the crossover treatment period).

The participant flow from REACH2 is shown in Appendix D.

REACH1

Of the 71 patients enrolled in the study, 68 (95.8%) discontinued study treatment with 24 patients (33.8%) discontinuing on or before Day 28. Adverse events and physician decision were the most frequently reported reasons for discontinuation on or before Day 28 (8 and 10 patients [11.3% and 14.1%], respectively) and at the end of the study (20 and 23 patients [28.2% and 32.4%], respectively). Of the 23 patients who discontinued ruxolitinib treatment due to physician decision, 6 patients discontinued because of clinical improvement including 4 patients in CR, 1 patient with VGPR and 1 patient with mixed response.

At the time of the DCO (5th June 2019) 24 patients (33.8%) remained in the study; 3 patients (4.2%) who were still receiving ruxolitinib were transferred to commercial product, and safety, disease assessment, and/or survival follow-up was discontinued for the 21 patients who were no longer receiving ruxolitinib. The remaining 47 patients had discontinued from the study because of death (44 patients, 62.0%) or patient decision (3 patients, 4.2%).

B.2.3.7. Baseline characteristics

The REACH2 study population (Table 9) represented patients ≥12 years of age with Grade II-IV steroid-refractory aGvHD. Baseline demographics were well-balanced between the two treatment arms. Mean age of patients in the ruxolitinib arm was 48.1 years (standard deviation [SD]: 16.30) and 50.9 years (SD:14.97) in the BAT arm. Overall, there were more male than female patients, but proportions were similar in both arms (ruxolitinib arm: 40.3% female, 59.7% male; BAT arm: 41.3% female, 58.7% male).

The REACH1 study population (Table 9) also represented patients ≥12 years of age with Grade II-IV steroid-refractory aGvHD. The majority of patients were <65 years of age, with a median age of 58 years (range: 18–73 years). Gender was evenly distributed (49.3% male and 50.7% female), and 93.0% of patients White/Caucasian.

Table 9: Baseline demographic and clinical characteristics – FAS, REACH2 and REACH1

	REACH2		REACH1
	Ruxolitinib n=154	**BAT n=155**	**Ruxolitinib N=71**
Age (years)			
n	154	155	71
Mean (SD)	48.1 (16.30)	50.9 (14.97)	52.9 (14.18)
Median	52.5	54.0	58.0
Q1-Q3	32.0–61.0	41.0–63.0	–
Min-max	12.0–73.0	13.0–71.0	18.0–73.0
Age category – n (%)			
Adolescents, 12 – <18 years	5 (3.2)	4 (2.6)	0
18–65 years	128 (83.1)	126 (81.3)	58 (81.7)
≥65 years	21 (13.6)	25 (16.1)	13 (18.3)
Sex			
Female	62 (40.3)	64 (41.3)	35 (49.3)
Male	92 (59.7)	91 (58.7)	36 (50.7)
Race – n (%)			
White	111 (72.1)	102 (65.8)	66 (93.0)
Black or African American	0	1 (0.6)	3 (4.2)
Asian	19 (12.3)	29 (18.7)	2 (2.8)
American Indian or Alaska native	NR	NR	0
Other	8 (5.2)	4 (2.6)	0
Unknown	16 (10.4)	19 (12.3)	0
Ethnicity – n (%)			
Hispanic/Latino	8 (5.2)	12 (7.7)	9 (12.7)
Not Hispanic/Latino	94 (61.0)	88 (56.8)	60 (84.5)
NR	29 (18.8)	36 (23.2)	2 (2.8)
Unknown	23 (14.9)	19 (12.3)	0
Weight (kg)			
n	150	152	71
Mean (SD)	67.5 (14.04)	66.2 (14.78)	78.64 (21.651)
Median	67.7	66.2	75.90

	REACH2		REACH1
	Ruxolitinib n=154	**BAT n=155**	**Ruxolitinib N=71**
Q1-Q3	58.0–78.0	54.6–74.5	–
Min-max	28.5–97.0	32.9–115.5	46.0–139.0
Height (cm)			
n	148	144	66
Mean (SD)	169.7 (9.86)	170.0 (10.16)	170.2 (10.64)
Median	170.0	170.0	170.0
Q1-Q3	161.9–177.5	163.0–177.0	–
Min-max	128.7–195.0	146.0–200.0	149.0–193.0
Body mass index (kg/m^2)			
n	146	142	66
Mean (SD)	23.4 (4.24)	22.7 (4.15)	26.83 (6.193)
Median	23.3	22.5	25.41
Q1-Q3	20.4–26.2	19.9–24.7	–
Min-max	13.5–34.4	13.9–35.7	18.4–46.6
Assessment of performance status – n (%)			
ECOG	NR	NR	70 (98.6)
Missing	NR	NR	1 (1.4)
ECOG performance status – n (%)			
0	NR	NR	3 (4.2)
1	NR	NR	24 (33.8)
2	NR	NR	25 (35.2)
3	NR	NR	17 (23.9)
4	NR	NR	1 (1.4)
Missing	NR	NR	1 (1.4)
Time from diagnosis of aGvHD Grade ≥2 (days)			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min-max	[redacted]	[redacted]	[redacted]
Overall severity of aGvHD at randomisation			
Grade 0	4 (2.6)	1 (0.6)	0
Grade I	2 (1.3)	0	0
Grade II	47 (30.5)	54 (34.8)	22 (31.0)
Grade III	70 (45.5)	67 (43.2)	33 (46.5)
Grade IV	31 (20.1)	33 (21.3)	16 (22.5)

	REACH2		REACH1
	Ruxolitinib n=154	BAT n=155	Ruxolitinib N=71
Prior systemic therapy for aGvHD†			
Steroid only	[redacted]	[redacted]	[redacted]
Steroid + CNI	[redacted]	[redacted]	[redacted]
Steroid + CNI + other systemic therapy	[redacted]	[redacted]	[redacted]
Steroid + other systemic therapy	[redacted]	[redacted]	[redacted]

Source: REACH2 final analysis CSR (50), REACH1 final analysis CSR (64), REACH1 additional listings (68).
Abbreviations: aGvHD, acute graft-versus-host-disease; BAT, best available therapy; cGvHD, chronic graft-versus-host-disease; CNI, calcineurin inhibitor; CSR, clinical study report; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; min, minimum; max, maximum; NR, not reported; Q, quartile; SD, standard deviation.

B.2.3.8. Prior and concomitant aGvHD therapies

A brief summary of prior and concomitant therapies in REACH2 and REACH1 is presented here. An overview of all prior and concomitant therapies is presented in Appendix M.

REACH2

All randomised patients (n=309, 100%) received at least corticosteroids (preferred term [PT] prednisolone, prednisone and methylprednisolone) as prior therapy and majority received a combination of prior steroids and other immunosuppressant such as “steroids + CNI” ([redacted]) or “steroid + CNI + other aGvHD systemic therapy” (as prophylaxis and/or treatment) ([redacted]). In total, [redacted] of patients in the ruxolitinib arm and [redacted] of patients in the BAT arm received only steroids as prior therapy (Table 9).

From randomisation up to EOT, concomitant medications were taken by 98.7% and 100% of patients in the ruxolitinib and in the BAT arms, respectively. The overall profile of concomitant medications was similar between the two treatment arms, with a few minor differences. In addition to corticosteroids and CNIs, the frequent concomitant medications also included agents for treatment of infections, gastric motility enhancers and electrolytes. With regards to immunosuppressive treatment, 85.5% and 82.0% of patients in the ruxolitinib and in the BAT arms, respectively, received CNIs from the time of randomisation. The most frequent CNI was cyclosporin (61.2% and 54.7%).

REACH1

All 71 participants had received prior systemic therapy with corticosteroids, including methylprednisolone, methylprednisolone sodium succinate, and prednisone. Other prior

systemic corticosteroids for GvHD in more than 1 patient included budesonide and triamcinolone.

All participants took at least 1 concomitant medication. The most frequently prescribed classes of concomitant medications were nucleosides and nucleotides excluding reverse transcriptase inhibitors (n=69, 97.2%), CNIs (n=63, 88.7%), and proton pump inhibitors and electrolyte solutions (n=60, 84.5% each).

B.2.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1. Analysis populations

The sets of analysis populations defined in REACH2 and REACH1 are presented in Table 10.

Table 10: Definition of analysis populations

Analysis populations	Definition	REACH2			REACH1	
		Ruxolitinib N=154 n (%)	BAT N=155 n (%)	Reported in submission	Ruxolitinib N=71 n (%)	Reported in submission
FAS / Efficacy evaluable population†	All randomised patients who signed the ICF	154 (100)	155 (100)	Yes	71 (100)	Yes
Safety set / Safety evaluable population†	All patients who received at least one dose of study treatment after randomisation	152 (98.7)	150 (96.8)	Yes	71 (100)	Yes
Per-protocol set	All patients from the FAS who were compliant with requirements of the clinical study protocol	[redacted]	[redacted]	No	N/A	N/A
Crossover analysis set	All patients randomised to and received BAT who then crossed over and received at least one dose of ruxolitinib	0	49 (31.6)	Yes (Appendix N)	N/A	N/A
PK analysis set / PK evaluable population†	All randomised patients who provided at least one evaluable PK concentration	152 (98.7)	48 (31.0)	Yes (Appendix N)	71 (100)	Yes (Appendix N)

Source: REACH2 final analysis CSR (50), REACH1 final analysis CSR (64).
† REACH1 terminology.
Abbreviations: BAT, best available therapy; CSR, clinical study report; FAS, full analysis set; ICF, informed consent form; N/A, not applicable; PK, pharmacokinetics.

B.2.4.2. Statistical analysis

An overview of statistical analyses for REACH2 and REACH1 is presented in Table 11.

Table 11: REACH2 and REACH1: Statistical analysis methods

	REACH2	REACH1
Statistical hypothesis	The primary efficacy analysis was the comparison of ORR at Day 28 between the two treatment arms. The following statistical hypotheses were tested to address the primary efficacy objective: H0: $ORR_{rux} \leq ORR_{BAT}$ vs H1: $ORR_{rux} > ORR_{BAT}$ where ORR_{rux} and ORR_{BAT} are the overall response rates at Day 28 in the ruxolitinib and BAT groups, respectively. The CMHchi-square test, stratified by the randomisation stratification factor (i.e. aGvHD Grade II vs III vs IV) was used to compare ORR between the 2 treatment groups, at the one-sided 2.5% level of significance	N/A
Statistical analysis	The primary efficacy variable was analysed at the time when all patients had completed their Day 56 visit or discontinued earlier. The primary analysis was performed on FAS according to ITT principle. ORR was summarised using descriptive statistics by treatment arm along with two-sided binomial 95% CIs. One sided p-value, odds ratio and 95% Wald confidence limits calculated from stratified Cochran-Mantel-Haenszel test were also presented	No formal statistical tests were performed. The primary efficacy endpoint was ORR at Day 28, defined as the proportion of patients demonstrating a response (CR, VGPR, or PR). The proportion of responders was calculated with 95% CIs for the efficacy evaluable population. Confidence intervals were calculated based on the exact method for binomial distributions. The key secondary endpoint, 6-month DOR was assessed when all patients had completed the 6-month (Day 180) visit, discontinued, or died. The 25th, 50th (median), and 75th percentiles for DOR were estimated, and the 95% CIs were calculated using the generalisation of Brookmeyer and Crowley's method with log-log transformation. The event-free probabilities for DOR (i.e. DOR in the absence of death or GvHD progression) at 6 months were estimated with 95% CIs calculated using Greenwood's formula to estimate the standard error
Sample size, power calculation	The study with a total of 309 patients and 1:1 randomisation (ruxolitinib vs BAT) stratified on aGvHD grade (Grade II vs Grade III vs Grade IV) would have 90% power to test for the primary endpoint (ORR at Day 28) and approximately 90% power to test	Approximately 70 patients were planned for the primary endpoint analysis. With the assumed true response rate of 60%, a sample size of 70 patients would provide >90% probability to have a 95% CI with a lower limit of ≥40%. The study was considered positive if

	REACH2	REACH1
	for the key secondary endpoint (durable ORR at Day 56). The family wise α-level would be controlled at 0.025 overall for the two comparisons. Specifically, this study would claim to have achieved the efficacy objective when the primary endpoint ORR at Day 28 showed a significant treatment effect at one-sided α=0.025. Conditional on significance of the primary endpoint, the key secondary endpoint durable ORR at Day 56 would be tested at one-sided α=0.025	≥37 out of 70 patients responded (i.e., if the lower limit of the 95% CI for ORR at Day 28 exceeded 40%)
Data management, patient withdrawals	Patients with missing assessments that prevented the evaluation of the primary endpoint were considered non-responders on that treatment arm. This included missing aGvHD response assessments at baseline and Days 28, 56. The following analysis windows were applied to the target day for assessments on overall response, where target day for Week X is X*7. Baseline assessment was the last aGvHD assessment prior to the date of randomisation (Day 1). A tolerance of up to 3 days from randomisation was considered in the analysis, but the baseline assessment would not be later than the date of treatment start. Weeks 1–8: –3 days/+3 days Weeks 12–24: –13 days/+14 days The analysis windows for assessments after crossover were similar, except that the baseline was the last aGvHD assessment prior to or on Crossover Day 1 (date of first administration of crossover treatment). No data imputation was applied	Patients who had missing response data at Day 28 (including withdrawals or deaths before Day 28) were considered to be non-responders

Source: REACH2 final analysis CSR (50), REACH2 SAP (67), REACH1 final analysis CSR (64).
Abbreviations: aGvHD, acute graft-versus-host-disease; BAT, best available therapy; BOR, best overall response; cGvHD, chronic graft-versus-host-disease; CI, confidence interval; CMH, Cochrane-Mantel-Haenszel; CR, complete response; CSR, clinical study report; FAS, full analysis set; FFS, failure-free survival; H, hypothesis; HR, hazard ratio; IA, interim analysis; ITT, intention-to-treat; N/A, not applicable; ORR, overall response rate; PR, partial response; rux, ruxolitinib; SAP, statistical analysis plan; VGPR, very good partial response.

B.2.5. Critical appraisal of the relevant clinical effectiveness evidence

Quality assessment of REACH2 was conducted using the NICE 7-item checklist for RCT (69), the full details of which are provided in Appendix D. Overall, REACH2 was found to have a very low risk of bias, with its only primary limitation being its open-label design. The strengths and limitations of the clinical effectiveness evidence are discussed in Section B.2.11.

B.2.6. Clinical effectiveness results of the relevant studies

A summary of efficacy data for the FAS (REACH2) and the efficacy evaluable population (REACH1) is presented in this section. Results from analyses performed on crossover sets (REACH2 only) and PK analysis sets are presented in Appendix N.

B.2.6.1. REACH2

B.2.6.1.1. Primary endpoint: Overall response rate at Day 28

REACH2 met its primary endpoint: ORR at Day 28 was higher in the ruxolitinib arm (62.3%) than in the BAT arm (39.4%). There was a statistically significant difference between the treatment arms (stratified Cochrane-Mantel-Haenszel (CMH) test p<0.0001, one-sided, odds ratio: 2.64 with 95% confidence interval [CI]: 1.65, 4.22). There was a higher proportion of complete responders in the ruxolitinib arm (34.4%) than in the BAT arm (19.4%) (Table 12). Additionally, the proportion of patients with a PR was 27.9% in the ruxolitinib group vs 20% in the BAT group.

At Day 28, the proportion of patients with no response was 4.5% in the ruxolitinib arm and 6.5% in the BAT arm. Progression of aGvHD was less common in the ruxolitinib arm (2.6%) than in the BAT arm (8.4%). Unknown responses due to death, early discontinuation or missing visits were also less common in the ruxolitinib arm (23.4%) than in the BAT arm (30.3%).

Table 12: Summary of ORR at Day 28 – REACH2, primary analysis, FAS

	Ruxolitinib N=154	BAT N=155
Responders, n (%)		
CR	53 (34.4)	30 (19.4)
PR	43 (27.9)	31 (20.0)

	Ruxolitinib N=154	BAT N=155
Non-responders, n (%)		
No response	7 (4.5)	10 (6.5)
Mixed response†	10 (6.5)	17 (11.0)
Progression	4 (2.6)	13 (8.4)
Other‡	1 (0.6)	7 (4.5)
Unknown/missing	36 (23.4)	47 (30.3)
Death	15 (9.7)	22 (14.2)
Early discontinuation	17 (11.0)	16 (10.3)
Missing visits	4 (2.6)	9 (5.8)
ORR: CR + PR, n (%)	96 (62.3)	61 (39.4)
95% CI	54.2, 70.0	31.6, 47.5
Odds ratio (95% CI)	2.64 (1.65, 4.22)	
p-value	<0.0001	

Source: REACH2 primary analysis CSR (70).
†Defined as improvement of at least 1 stage in the severity of GvHD in at least one organ accompanied by progression in another organ or development of signs or symptoms of GvHD in a new organ. ‡Patients with additional systemic therapies along with CR/PR per investigator assessment.
Abbreviations: BAT, best available therapy; CI, confidence interval; CR, complete response; CSR, clinical study report; FAS, full analysis set; GvHD, graft-versus-host-disease; N/A, not applicable; ORR, overall response rate; PR, partial response.

B.2.6.1.1.1 Sensitivity analysis of primary endpoint

Sensitivity analysis performed using the Fisher's exact method confirmed the results of the primary analysis, with an odds ratio of 2.55 (95% CI: 1.61, 4.03; p<0.0001).

B.2.6.1.2. Secondary Endpoints

B.2.6.1.2.1 Durable ORR at Day 56

In REACH2, durable ORR at Day 56 as of the primary analysis cut-off, showed a statistically significant difference between the two arms and was in favour of ruxolitinib (39.6% in the ruxolitinib arm vs 21.9% in the BAT arm; odds ratio: 2.38; 95% CI: 1.43, 3.94; p=0.0005) (Table 13).

Table 13: Durable ORR at Day 56 – REACH2, primary analysis, FAS

	Ruxolitinib N=154	BAT N=155
Responders, n (%)		
CR	41 (26.6)	25 (16.1)
PR	20 (13.0)	9 (5.8)
Non-responders, n (%)		
No response	1 (0.6)	1 (0.6)
Mixed response†	5 (3.2)	4 (2.6)
Progression	0	0
Other‡	0	1 (0.6)
Unknown/missing	29 (18.8)	21 (13.5)
Death	7 (4.5)	2 (1.3)
Early discontinuation	13 (8.4)	15 (9.7)
Missing visits	9 (5.8)	4 (2.6)
ORR: CR + PR, n (%)	61 (39.6)	34 (21.9)
95% CI	(31.8, 47.8)	(15.7, 29.3)
Odds ratio (95% CI)	2.38 (1.43,3.94)	
p-value	0.0005	

Source: REACH2 primary analysis CSR (70).
†Defined as improvement of at least 1 stage in the severity of GvHD in at least one organ accompanied by progression in another organ or development of signs or symptoms of GvHD in a new organ. ‡Patients with additional systemic therapies along with CR/PR per investigator assessment.
Abbreviations: BAT, best available therapy; CR, complete response; CSR, clinical study report; FAS, full analysis set; GvHD, graft-versus-host-disease; ORR, overall response rate; PR, partial response.

B.2.6.1.2.2 Best overall response

The best overall response (BOR) up to Day 28 was higher in the ruxolitinib arm (81.8%; 95% CI: 74.8, 87.6) than in the BAT arm (60.6%; 95% CI: 52.5, 68.4). There was a statistically significant difference between the ruxolitinib and BAT arms (p<0.0001) with the odds ratio of 3.07 (95% CI: 1.80, 5.25) for response in the ruxolitinib arm compared with the BAT arm. By Day 28, the proportion of patients with no response was lower in the ruxolitinib arm (8.4%) than in the BAT arm (13.5%), and progression of aGvHD was also more frequent in the BAT arm (6.5%) than in the ruxolitinib arm (2.6%). More patients in the BAT arm had a mixed response (9.0%) than in the ruxolitinib arm (4.5%).

B.2.6.1.2.3 Duration of response

The median duration of response (DOR) was longer in the ruxolitinib arm (167 days, range: 22 to 677) than in the BAT arm (106 days, range: 10–526). The probability of an event (progression or addition of systemic therapy for aGvHD) with longer follow-up data at 6 months was [redacted] in the ruxolitinib arm than in the BAT arm ([redacted]; 95% CI: [redacted] vs [redacted]%; 95% CI: [redacted]). A similar trend was observed at 12 months ([redacted]%; 95% CI: [redacted]%; 95% CI: [redacted]).

B.2.6.1.2.4 Overall survival

The Kaplan-Meier (KM)-estimated median OS was longer in the ruxolitinib arm (10.71 months) than in the BAT arm (5.82 months). There was a 15% reduction in the risk of death in the ruxolitinib arm relative to the BAT arm (HR: 0.85; 95% CI: 0.63, 1.14), although not statistically significant (log-rank p-value: 0.2800) (Figure 6).

The OS analysis was performed using longer follow-up data, up to the end of study, including 89 deaths (57.8%) in the ruxolitinib arm and 91 deaths (58.7%) in the BAT arm. Although data were available for up to 24 months after randomisation, 3 patients had longer follow-up data (up to 36 months) available for OS analysis (as well as FFS and EFS analysis, Section B.2.6.1.2.5 and Section B.2.6.1.2.10) for the following reasons:

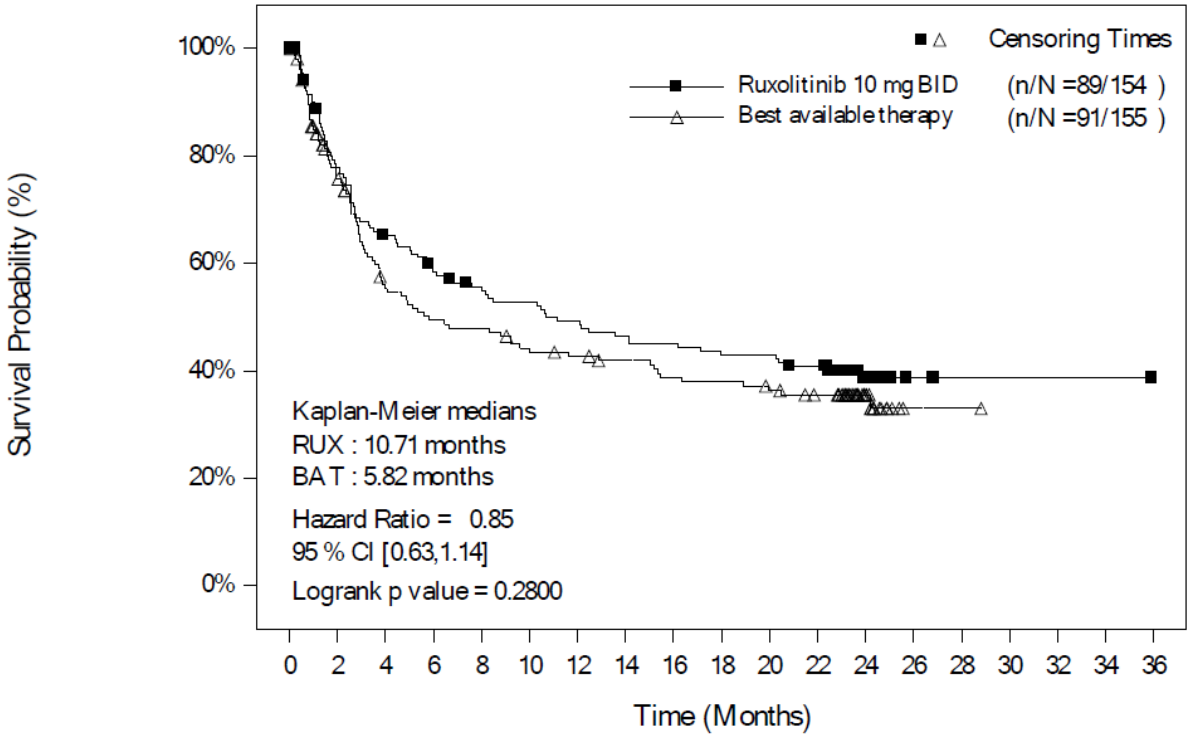
[redacted]

Crossover adjustment

In total, 49 patients in the BAT arm (32%) crossed over to ruxolitinib during the randomised treatment period. As crossover may bias estimates of survival, estimates of time to death were adjusted in patients who crossed over, using the two-stage method recommended in

NICE Decision Support Unit (DSU) technical support document (TSD) 16 to adjust survival times for treatment switching (71), as described in Appendix O. In the BAT arm, median OS adjusted for crossover was [redacted] months, resulting in an adjusted HR of [redacted] (95% CI: [redacted]), or [redacted] in the risk of death in the ruxolitinib arm vs the BAT arm, [redacted] (log-rank p-value: [redacted]). The OS curves adjusted for crossover are presented in Figure 7.

Figure 6: Kaplan-Meier curves of OS – REACH2, final analysis, FAS



No. of patients still at risk

Time(Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36
Ruxolitinib 10 mg BID	154	116	96	85	79	75	70	66	64	61	61	57	24	2	1	1	1	1	0
Best available therapy	155	107	75	67	65	58	56	53	49	48	45	41	17	1	1	0	0	0	0

Source: REACH2 final analysis CSR (50).
Abbreviations: BAT, best available therapy; BID, twice a day; CI, confidence interval; CSR, clinical study report; FAS, full analysis set; OS, overall survival; RUX, ruxolitinib.

Figure 7: OS curves adjusted for crossover – REACH2, final analysis, FAS

Abbreviations: BID, twice a day, FAS, full analysis set; OS, overall survival.

B.2.6.1.2.5 Failure-free survival

Median FFS with ruxolitinib was statistically significantly longer than with BAT (4.86 months vs 1.02 months; HR: 0.51, 95% CI: 0.39, 0.66; p<0.0001) (Figure 8). The estimated incidence rate of an FFS event at 1 month (cut-off for primary analysis), was lower in the ruxolitinib arm (17.92%; 95% CI: 12.26, 24.46) than in the BAT arm (49.13%; 95% CI: 40.94, 56.80). With additional follow up data, the trend remained the same over subsequent time points, although the estimated event rate increased in both treatment arms.

Figure 8: Kaplan-Meier plot of FFS – REACH2, final analysis, FAS

Source: REACH2 final analysis CSR (50).
Abbreviations: BAT, best available therapy; BID, twice a day; CI, confidence interval; CSR, clinical study report; FAS, full analysis set; FFS, failure-free survival; RUX, ruxolitinib.

B.2.6.1.2.6 Incidence of malignancy relapse/progression

Among the 147 patients in each treatment arm who had malignant haematological disease at baseline, events of malignancy relapse/progression occurred in a similar proportion of patients in both treatment arms (13.6% in the ruxolitinib arm and 17.0% in the BAT arm) at the end of study. Since the primary analysis, there were six additional patients in the ruxolitinib arm and five additional patients in the BAT arm with events of malignancy relapse/progression. In the final analysis, there was a high percentage of patients with competing risks in both the ruxolitinib and BAT arms, with deaths occurring in 46.3% and 45.6% of patients, respectively, and heavy censoring (40.1% and 37.4% of patients, respectively). The probability of malignancy relapse/progression was relatively low in both treatment arms over the duration of the study (Figure 9).

Figure 9: Cumulative incidence curve of malignancy relapse/progression– REACH2, final analysis, FAS

Source: REACH2 final analysis CSR (50).
Abbreviations: BID, twice a day; CSR, clinical study report; FAS, full analysis set; NA, not applicable.

B.2.6.1.2.7 Non-relapse mortality

The analysis of NRM among all FAS patients included 46.8% of patients with events in the ruxolitinib arm and 45.8% of patients in the BAT arm. The cumulative incidence curves for NRM were overlapping for the ruxolitinib and BAT arms, indicating similar event rates between the arms over time (Figure 10). The competing risk (haematological disease relapse/progression) was low in both ruxolitinib and BAT arms (13.6% and 16.1%, respectively). However, censoring was high in both ruxolitinib and BAT arms (39.6% and 38.1%, respectively), implying a high proportion of patients were alive and had no relapse/progression.

Figure 10: Cumulative incidence curve of NRM – REACH2, final analysis, FAS

Source: REACH2 final analysis CSR (50).
Abbreviations: BID, twice a day; CSR, clinical study report; FAS, full analysis set; NA, not applicable; NRM, non-relapse mortality.

B.2.6.1.2.8 Patient-reported outcomes

The EQ-5D-5L and Functional Assessment of Cancer Therapy – Bone Marrow Transplant (FACT-BMT) questionnaires completion rates, as a percentage of available patients, were similar between the two arms throughout the study. There was a decrease in number of patients available for evaluation with time. Baseline scores were similar between the two treatment arms. In both the randomised treatment and crossover periods,

. The mean FACT-BMT total score at baseline in the ruxolitinib arm ( ) and in the BAT arm (at Week 24 to and , respectively. The mean EQ-5D-5L score at baseline in the ruxolitinib arm ( ) and in the BAT arm (at Week 24 to and , respectively. The mean EQ-5D-5L visual analogue score (VAS) score for 'your health today'

at baseline in the ruxolitinib arm ([redacted]) and in the BAT arm ([redacted]) [redacted] at Week 24 to [redacted] and [redacted], respectively.

B.2.6.1.2.9 Cumulative steroid dosing

At Day 56, more patients in the ruxolitinib arm (22.1%; 95% CI: 15.8, 29.5) had completely tapered off corticosteroids than in the BAT arm (14.8%; 95% CI: 9.6, 21.4) with an odds ratio of 1.63 (95% CI: 0.91, 2.92). Most patients in both treatment arms (ruxolitinib and BAT) had any dose reduction (91.6% and 87.1%) or at least 50% dose reduction (76% and 71.6%) of corticosteroids by Day 56. The dose reduction achieved at Day 56 was [redacted] in patients in the ruxolitinib arm than in the BAT arm [redacted] vs [redacted] maximum reduction: [redacted] vs [redacted]).

The trend seen at Day 56 continued until EOT. More patients in the ruxolitinib arm (43.5%; 95% CI: 35.5, 51.7) had completely tapered off corticosteroids than in the BAT arm (31.6%; 95% CI: 24.4, 39.6) with odds ratio of 1.67 (95% CI: 1.05, 2.65). Most patients in both treatment arms (ruxolitinib and BAT) had any dose reduction (92.2% and 87.1%) or at least 50% dose reduction (77.3% and 74.2%) of corticosteroids by EOT. The dose reduction achieved at EOT was [redacted] in patients in the ruxolitinib arm than the BAT arm (–61.6% vs –50.7%; maximum reduction: [redacted]

B.2.6.1.2.10 Event-free survival

The EFS analysis at the end of study included 94 (61%) events in the ruxolitinib arm and 96 (61.9%) events in the BAT arm. The KM-estimated median EFS was longer in the ruxolitinib arm (8.28 months) than in the BAT arm (4.17 months) (Figure 11). There was a 15% reduction in risk of EFS event in the ruxolitinib arm relative to the BAT arm (HR: 0.85; 95% CI: 0.64, 1.13), which was not statistically significant (log-rank p-value: [redacted]).

Figure 11: Kaplan-Meier curves of EFS – REACH2, final analysis, FAS

Source: REACH2 final analysis CSR (50).
Abbreviations: BAT, best available therapy; BID, twice a day; CI, confidence interval; CSR, clinical study report; EFS, event-free survival; FAS, full analysis set; RUX, ruxolitinib.

B.2.6.1.2.11 Incidence of cGvHD

Up to the end of study, 33.8% of patients in the ruxolitinib arm and 21.9% of patients in the BAT arm had developed cGvHD. The proportion of patients with competing risks was similar between the ruxolitinib arm (51.9%) and the BAT arm (54.8%).

The estimated cumulative incidence rate of cGvHD increased with time in both treatment arms. At 6 months, the probability of cGvHD was [redacted] ([redacted]%; 95% CI: [redacted] in the ruxolitinib arm and [redacted] 95% CI: [redacted] in the BAT arm) (Figure 12). However, in the subsequent timepoints at 12 months, 18 months and 24 months, the probability of cGvHD was [redacted] in the ruxolitinib arm than in the BAT arm ([redacted]% vs [redacted]%, [redacted]% vs [redacted]% and [redacted]% vs [redacted]%, respectively).This is reflected in the economic model, where a higher proportion of patients in the ruxolitinib arm are modelled to go on to develop cGvHD (Section B.3.2.2).

The median onset time of cGvHD was [redacted] in the ruxolitinib arm ([redacted] days) than in the BAT arm (185 days). Also, the majority of cGvHD events were [redacted] at time of onset in [redacted] and there were [redacted] cases of severe cGvHD in the ruxolitinib arm ([redacted] patients) than in the BAT arm ([redacted] patients).

Figure 12: Cumulative incidence of cGvHD – REACH2, final analysis, FAS

Source: REACH2 final analysis CSR (50).
Abbreviations: BID, twice a day; cGvHD, chronic graft-versus-host-disease; CSR, clinical study report; FAS, full analysis set; NA, not applicable.

B.2.6.1.2.12 Exploratory efficacy results

Resource utilisation

The proportion of patients who initiated study treatment while being hospitalised was similar between the two treatment arms. Median duration of hospital stay in the bone marrow transplant unit was higher in the BAT arm (42 days, interquartile range [IQR]: 24–67) than in the ruxolitinib arm (32.5 days, IQR: 8–53). Most patients required hospitalisation either in a bone marrow transplant unit (ruxolitinib arm: 16.9% and BAT arm: 12.9%) or the general ward (ruxolitinib arm: 14.9% and BAT arm: 20.6%).

The proportion of patients who were re-admitted to hospital (bone marrow transplant unit) was [redacted] (ruxolitinib arm: [redacted]% and BAT arm: [redacted]%). [redacted] patients in the BAT arm ([redacted]%) were re-admitted to a general ward than in the ruxolitinib arm ([redacted]%). The median duration of stay at re-admission was [redacted] (ruxolitinib arm and BAT arm), whether re-admitted to the bone marrow unit ([redacted] days, IQR: [redacted] and [redacted] days, IQR: [redacted]) or the general ward ([redacted] days, IQR: [redacted] and [redacted] days, IQR: [redacted]).

B.2.6.2. REACH1

B.2.6.2.1. Primary endpoint: Overall response rate at Day 28

The study achieved the predetermined threshold for a positive study outcome (lower limit of the 95% CI for Day 28 ORR ≥40%), with 56.3% of patients (95% CI: 44.0, 68.1) demonstrating a response at Day 28, including 26.8% of patients who achieved a CR and 8.5% of patients who achieved a VGPR (Table 14).

Table 14: Summary of ORR at Day 28 – REACH1, final analysis, efficacy evaluable population

	Ruxolitinib N=71
Responders, n (%)	
CR	19 (26.8)
PR	6 (8.5)
VGPR	15 (21.1)
Non-responders, n (%)	
No response	2 (2.8)
Mixed response†	3 (4.2)
Progression	2 (2.8)
Other‡	1 (1.4)
Unknown/missing	23 (32.4)
Death	10 (14.1)
Early discontinuation	12 (16.9)
Missing visits	1 (1.4)
ORR: CR + PR, n (%)	40 (56.3)
95% CI	(44.0, 68.1)

Source: REACH1 final analysis CSR (64).
†Defined as improvement of at least 1 stage in the severity of GvHD in at least one organ accompanied by

progression in another organ or development of signs or symptoms of GvHD in a new organ. ‡Patients with additional systemic therapies along with CR/PR per investigator assessment.
Abbreviations: BAT, best available therapy; CI, confidence interval; CR, complete response; CSR, clinical study report; FAS, full analysis set; GvHD, graft-versus-host-disease; N/A, not applicable; ORR, overall response rate; PR, partial response; VGPR, very good partial response.

B.2.6.2.2. Secondary endpoints

B.2.6.2.2.1 Duration of response at 6 months

For patients who had a response at any timepoint, median DOR at 6 months was 345 days (95% CI: 154.0, NE). The 6-month event-free probabilities for DOR based on a response at any timepoint was 62.1% (95% CI: 45.8, 74.8). For patients who had a response at Day 28, the median DOR was 669.0 days (95% CI: 159.0, NE) with a median follow-up time of 195.0 days (range: 7–805 days). The 6-month event-free probability for DOR based on a response at Day 28 was 68.2% (95% CI: 49.6, 81.2) and was numerically greater than that reported for patients who responded at any time (Table 15).

Table 15: DOR at 6 months – REACH1, final analysis, efficacy evaluable population

	Ruxolitinib N=71	
	Response at any time point	**Response at Day 28**
Patients who had a response at the specified time point, n (%)	54 (76.1)	40 (56.3)
Patients with events, n (%)	23 (42.6)	16 (40.0)
Progression of disease	7 (13.0)	5 (12.5)
Death	16 (29.6)	11 (27.5)
Duration of response, days (95% CI)		
25th percentile	96.0 (29.0, 159.0)	154.0 (29.0, 326.0)
50th percentile (median)	345.0 (154.0, NE)	669.0 (159.0, NE)
75th percentile	NE (669.0, NE)	NE (669.0, NE)
Event-free probability estimates at 6-month (95% CI)	62.1 (45.8, 74.8)	68.2 (49.6, 81.2)
Follow-up time, days		
Median	128.5	195.0
Min, max	3.0, 805.0	7.0, 805.0

Source: REACH1 final analysis CSR (64).
Abbreviations: CI, confidence interval; CSR, clinical study report; DOR, duration of response; min, minimum; max, maximum; NE, not estimated.

B.2.6.2.2.2 Other secondary endpoints

Results from other secondary endpoints (3-month DOR, FFS, ORR and OS) for REACH1 are presented in Appendix N.

B.2.6.3. Real world evidence

The efficacy and safety evidence for ruxolitinib in GvHD is further strengthened by real-world evidence (RWE).

Findings from a compassionate use program of ruxolitinib in patients with acute and chronic GvHD showed a BOR of Grade 0 or I disease in 56% of patients with aGvHD (72). Furthermore, corticosteroid usage was substantially reduced in patients who received ruxolitinib: the tapering off or reduction in corticosteroid dosage was possible in over 83% of patients overall. Among patients with aGvHD, 91% were taking corticosteroids at baseline; this decreased to 64% during ruxolitinib treatment.

Additionally, a study looked at data collected during the COVID-19 pandemic, when ruxolitinib was commissioned by NHSE for the treatment of acute and chronic GvHD (n=48 and n=134, respectively), as a way of reducing hospital attendances. The study found high response rates in patients treated with ruxolitinib, with ORRs of 71% for patients with aGvHD (at Day 56) (30). It must be noted, however, that ruxolitinib was permitted in combination with other agents, and therefore responses could be attributable to concomitant treatments. In terms of safety, ruxolitinib was well tolerated with low rates of dose modification (15%) and discontinuation (10%) for toxicity, lower than those observed in the REACH trials.

B.2.7. Subgroup analyses

This submission covers the full population of the planned marketing authorisation. Pre-specified subgroup analyses of the primary endpoints of REACH2 and REACH1 are presented in Appendix E.

B.2.8. Meta-analysis

Direct trial data comparing ruxolitinib to BAT were available from REACH2, therefore a pairwise meta-analysis was not needed.

B.2.9. Indirect and mixed treatment comparisons

Direct trial data comparing ruxolitinib to BAT were available from REACH2, therefore an indirect treatment comparison was not conducted.

B.2.10. Adverse reactions

Across REACH2 and REACH1, ruxolitinib was generally well-tolerated in patients with SR-aGvHD. In general, the safety profile of ruxolitinib was consistent with that previously observed in patients with myelofibrosis and polycythaemia vera, and no unexpected toxicities were observed with ruxolitinib therapy, with the assigned dose of 10 mg BID tolerable. The UK clinicians consulted as part of the submission stated that they had no concerns with the safety data from the REACH trials and that the toxicity profile of ruxolitinib compared well with other treatments for SR-aGvHD (9).

B.2.10.1. REACH2

B.2.10.1.1. Overview of adverse events

There was a significant difference in duration of exposure between the two treatment groups (median exposure: 63 days (range: 6.0–678.0) in the ruxolitinib arm vs 29 days (range: 1.0–188.0) in the BAT arm, partly because patients on BAT were allowed to cross over to ruxolitinib after Day 28 and there were higher discontinuations during the treatment period in the BAT arm (87.1%) than in the ruxolitinib arm (77.3%). Therefore, the AE profile in the ruxolitinib arm is reflective of the longer treatment duration. The data presented in Table 16 should therefore be interpreted with caution given the differences in the duration of exposure between the two treatment groups as specified above; due to that expected imbalance in exposure, safety summaries for the randomised treatment were produced for the following periods, unless specified:

- Up to Day 31 (the upper bound of the Day 28 visit window)
- Up to either cut-off date, or end date of on-randomised-treatment period, whichever was earlier

Up to Day 28, a [redacted] (ruxolitinib vs BAT) experienced at least one AE ([redacted]% vs [redacted]%). The incidence of all AEs, serious AEs (SAE), fatal SAEs and AEs requiring additional therapies was [redacted]. The incidence of treatment-related AEs, AEs leading to discontinuation and AEs leading to dose adjustment/interruption were [redacted] in the ruxolitinib arm than in the BAT arm (Table 16).

In the randomised treatment period, [redacted] experienced at least one AE ([redacted]% vs [redacted]%). The overall AE profile during the randomised treatment period remained consistent with that at Day 28 except for SAEs that were [redacted] in the ruxolitinib arm ([redacted]%) than in the BAT arm ([redacted]%) (Table 16).

Table 16: Overview of adverse events – REACH2, final analysis, safety set

	Up to Day 28				Randomised treatment period			
	Ruxolitinib N=152		BAT N=150		Ruxolitinib N=152		BAT N=150	
	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
All AEs	[redacted]							
Treatment-related	[redacted]							
SAEs	[redacted]							
Treatment-related	[redacted]							
Fatal SAEs	[redacted]							
Treatment-related	[redacted]							
AEs leading to discontinuation	[redacted]							
Treatment-related	[redacted]							
AEs leading to study treatment dose adjustment /interruption	[redacted]							
AEs requiring additional therapy	[redacted]							

Source: REACH2 final analysis CSR (50).
Abbreviations: AE, adverse event; BAT, best available therapy; CSR, clinical study report; SAE, serious adverse event.

B.2.10.1.2. Adverse events suspected to be related to study treatment

Up to Day 28, the most frequent AEs by PT (all grades) suspected to be related to study treatment (≥4% of patients) in the ruxolitinib arm were those of cytopenia including thrombocytopenia ([redacted]%), anaemia ([redacted]%), platelet count decreased ([redacted]%), neutropenia ([redacted]%), white blood cell (WBC) count decreased ([redacted]%), neutrophil count decreased ([redacted]%)

and leukopenia ([redacted]%), followed by CMV infection reactivation ([redacted]%). Similarly, Grade ≥3 AEs suspected to be related to ruxolitinib were also cytopenias, with the most frequent PTs including thrombocytopenia ([redacted]%), platelet count decreased ([redacted]%), anaemia ([redacted]%), neutropenia ([redacted]%), WBC count decreased ([redacted]%) and neutrophil count decreased ([redacted]%). Based on the known safety profile of ruxolitinib and as expected in the study population, cytopenias are frequently reported events. In the BAT arm, the most frequent AEs by PT (all grades) suspected to be related to study treatment (≥4% of patients) were those of cytopenia, including platelet count decreased ([redacted]%), WBC count decreased ([redacted]%) and thrombocytopenia ([redacted]%), followed by CMV infection reactivation ([redacted]%). The most frequent Grade ≥3 AEs suspected to be related to study treatment in the BAT arm were platelet count decreased ([redacted]%), thrombocytopenia ([redacted]%) and WBC count decreased ([redacted]%) (Appendix F).

During the randomised treatment period, in the ruxolitinib arm, the most frequent AEs by PT (all grades) suspected to be related to study treatment (in ≥5% of patients) were those of cytopenia, including thrombocytopenia ([redacted]%), anaemia ([redacted]%), platelet count decreased ([redacted]%), neutropenia ([redacted]%), WBC count decreased [redacted]%), neutrophil count decreased ([redacted]%), leukopenia ([redacted]%), as well as CMV infection (combined for PTs CMV infection reactivation: [redacted]% and CMV infection: [redacted]%). Similarly, most frequent Grade ≥3 AEs suspected to be related to ruxolitinib were those of cytopenia, including thrombocytopenia ([redacted]%), anaemia ([redacted]%), platelet count decreased ([redacted]%), neutropenia ([redacted]%), WBC count decreased ([redacted]%), neutrophil count decreased ([redacted]%) and leukopenia ([redacted]%). In the BAT arm, the most frequent AEs by PT (all grades) suspected to be related to study treatment (in ≥5% of patients) were CMV infection (combined for PTs CMV infection reactivation: [redacted]% and CMV infection: [redacted]%), followed by those of cytopenia, including WBC count decreased [redacted]%), anaemia ([redacted]%) and platelet count decreased [redacted]%). Grade ≥3 AEs suspected to be related to study treatment in the BAT arm were primarily cytopenia PTs, including WBC decreased ([redacted]%) and platelet count decreased [redacted]%) (Appendix F).

B.2.10.1.3. Serious Adverse Events

Up to Day 28, a similar proportion of patients in the ruxolitinib arm ([redacted]%) and in the BAT arm ([redacted]%) experienced an SAE. The incidence of Grade ≥3 SAEs was [redacted]% in the ruxolitinib arm and 31.3% in the BAT arm. In the ruxolitinib arm, sepsis ([redacted]%) was the only Grade ≥3 SAE by PT observed in >5% of patients. In the BAT arm, CMV infection

reactivation ([redacted]%), septic shock ([redacted]%) and respiratory failure ([redacted]%) were the most frequent Grade ≥3 SAE by PT (Table 17).

During the randomised treatment period, SAEs were observed in [redacted]% of patients in the ruxolitinib arm and [redacted]% in the BAT arm. The proportion of patients with Grade ≥3 SAEs was higher in the ruxolitinib arm ([redacted]%) than the BAT arm ([redacted]%). In the ruxolitinib arm, sepsis ([redacted]%), septic shock [redacted]%) and diarrhoea (5.3%) were the only Grade ≥3 SAEs by PT observed in ≥5% of patients. In the BAT arm, sepsis [redacted]%), septic shock ([redacted]%), pneumonia ([redacted]%) and CMV infection (combined for PTs CMV infection reactivation: [redacted]% and CMV infection: [redacted]%) were the only Grade ≥3 SAEs by PT occurring in ≥5% of patients (Table 17).

Table 17: Serious AEs by PT, occurring in ≥2% of patients in either arm, in either time period – REACH2, final analysis, safety set

	Up to Day 28				Randomised treatment period			
	Ruxolitinib N=152		BAT N=150		Ruxolitinib N=152		BAT N=150	
	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
Number of patients with at least one event	[redacted]							
Abdominal pain	[redacted]							
Acute kidney injury	[redacted]							
Acute respiratory failure	[redacted]							
Bacteraemia	[redacted]							
Blood bilirubin increased	[redacted]							
CMV colitis	[redacted]							
CMV infection	[redacted]							
CMV infection reactivation	[redacted]							
Confusional state	[redacted]							
Diarrhoea	[redacted]							

	Up to Day 28				Randomised treatment period			
	Ruxolitinib N=152		BAT N=150		Ruxolitinib N=152		BAT N=150	
	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
Febrile neutropenia	[redacted]							
GvHD	[redacted]							
Multiple organ dysfunction syndrome	[redacted]							
Neutropenia	[redacted]							
Pancytopenia	[redacted]							
Platelet count decreased	[redacted]							
Pneumonia	[redacted]							
Pseudomonal sepsis	[redacted]							
Pyrexia	[redacted]							
Renal failure	[redacted]							
Respiratory failure	[redacted]							
Sepsis	[redacted]							
Septic shock	[redacted]							

Source: REACH2 final analysis CSR (50).
Abbreviations: AE, adverse event; BAT, best available therapy; CMV, cytomegalovirus; CSR, clinical study report; GvHD, graft-versus-host-disease; PT, preferred term.

B.2.10.1.4. Deaths

During the randomised treatment period, a similar proportion of patients died in the ruxolitinib arm (58.6%) and in the BAT arm (59.3%). Deaths due to aGvHD (including aGvHD and/or complications attributed to treatment for aGvHD) occurred in 25% of patients in the ruxolitinib arm and 25.3% of patients in the BAT arm. In the ruxolitinib arm, the other frequent causes of death were sepsis and multiple organ dysfunction syndrome (3.3% each), underlying haematological disease progression (2.6%) and septic shock (2.0%). In the BAT

arm, the other frequent causes of death were: sepsis (3.3%), respiratory failure (2.7%), multiple organ dysfunction syndrome, septic shock and AML recurrent (2.0% each).

On-treatment deaths

On-randomised treatment deaths were defined as deaths from date of first administration of randomised treatment to 30 days after the last administration of randomised treatment. Up to Day 28, there were fewer on-treatment deaths in the ruxolitinib arm (9.9%) than in the BAT arm (14.0%). Up to the final database lock, on-treatment deaths occurred in 28.3% and 24.0% of patients in the ruxolitinib and in the BAT arms, respectively. The most common cause of death was the study indication (including aGvHD and/or complications attributed to treatment for aGvHD) in both the ruxolitinib (13.8%) and the BAT arms (14.0%).

SAEs with fatal outcomes

Up to Day 28, the proportions of patients with SAEs with fatal outcome were similar between the two treatment arms (7.9% in the ruxolitinib arm and 11.3% in the BAT arm). A total of 3.9% of patients in the ruxolitinib arm and 8.7% of patients in the BAT arm had fatal SAEs due to the study indication. The majority of the fatal SAEs up to Day 28 were not suspected to be related to study treatment. During the randomised treatment period, SAEs with fatal outcome occurred in similar proportions of patients in both treatment arms (ruxolitinib arm: 21.7%; BAT arm: 21.3%). Sepsis (5.3%) and septic shock (4.6%) were the most common SAEs with a fatal outcome in the ruxolitinib arm (≥2%). The most common SAEs with a fatal outcome in the BAT arm (≥2%) were: sepsis, septic shock, respiratory failure, pneumonia (2.7% each) and multiple organ dysfunction syndrome, GvHD (2.0% each).

B.2.10.2. REACH1

A summary of safety in the REACH1 trial is presented in Appendix F.

B.2.11. Interpretation of clinical effectiveness and safety evidence

Ruxolitinib is a Janus kinase 1 (JAK1) and 2 (JAK2) inhibitor indicated for the treatment of patients with aGvHD following alloSCT, aged 12 years and over who have inadequate response to corticosteroids. The EBMT recommends ruxolitinib as the new standard of care for primary treatment for SR-aGvHD (26), which aligns with the proposed positioning of ruxolitinib in the treatment pathway for SR-aGvHD within this submission. Notably, the

BSBMTCT strongly recommend that ruxolitinib should be made available equitably across the UK for patients with SR-GvHD (27).

Efficacy

Results from the pivotal Phase 3 REACH2 trial provide evidence for the clinical efficacy of ruxolitinib for treating SR-aGvHD in patients aged 12 years and older, and are supported by the results from the Phase 2 trial, REACH1. The results consistently demonstrate clinically meaningful improvements with ruxolitinib across a range of efficacy endpoints, including response rates and FFS.

REACH2 met its primary endpoint: ruxolitinib provided clinically meaningful and statistically significant improvements relative to BAT in terms of ORR (62.3% vs 39.4%; odds ratio 2.64 with 95% CI: 1.65, 4.22; p<0.0001, one-sided). The clinically meaningful benefit of ruxolitinib was further demonstrated by results from the key secondary endpoint, durable ORR at Day 56, which also showed a statistically significant difference between the two arms in favour of ruxolitinib (39.6% in the ruxolitinib arm vs 21.9% in the BAT arm; odds ratio: 2.38; 95% CI: 1.43, 3.94; p=0.0005). Additionally, FFS with ruxolitinib was statistically significantly longer than with BAT (median FFS: 4.86 months vs 1.02 months; HR: 0.51, 95% CI: 0.39, 0.66; p<0.0001).

The OS analysis was performed using data up to the end of study, including 89 deaths (57.8%) in the ruxolitinib arm and 91 deaths (58.7%) in the BAT arm. The analysis supported the trend of longer median OS in the ruxolitinib arm compared with the BAT arm by approximately 5 months, despite crossover between the arms (10.71 months in the ruxolitinib arm vs 5.82 months in the BAT arm). As the rate of crossover between the ruxolitinib and BAT arms is an issue which affects OS, a method adjusting survival for treatment switching (as described in Appendix O) was applied to patients who had crossed over from BAT to the ruxolitinib arm. The resulting median OS adjusted for crossover in the BAT arm was slightly [redacted] than the unadjusted median OS ([redacted] months vs 5.82 months; median OS in ruxolitinib arm: 10.71 months).

One of the significant unmet needs of patients with aGvHD is for an alternative treatment which can reduce the use of corticosteroids, and therefore reduce steroid-related toxicity, as confirmed by UK clinicians (9). Ruxolitinib addresses this unmet need, as seen in REACH2, with more patients in the ruxolitinib arm (22.1%) completely tapering off corticosteroids at Day 56 than in the BAT arm (14.8%). The dose reduction achieved at Day 56 was [redacted] in

patients in the ruxolitinib arm than the BAT arm [redacted]% vs [redacted]%; maximum reduction: –[redacted]% vs [redacted]%). A similar trend was seen for complete tapering and reductions of steroid dosing until EOT.

Whether disease- or treatment-related, the symptoms experienced by patients with aGvHD following alloSCT significantly affect their HRQoL. Clinicians have confirmed that improving patients' quality of life was a significant unmet need for patients in the acute setting (9). In REACH2, there was [redacted] in HRQoL, as measured by EQ-5D-5L and FACT-BMT questionnaires, in the ruxolitinib arm than in the BAT arm. The mean FACT-BMT total score at baseline in the ruxolitinib arm ([redacted]) and in the BAT arm ([redacted]) [redacted] at Week 24 to [redacted] and [redacted], respectively.

Data from the Phase 2 trial REACH1 provide further evidence for the clinical efficacy of ruxolitinib in patients aged 12 years and older with SR-aGvHD. Similar to REACH2, REACH1 met its primary endpoint of ORR at Day 28, by achieving the predetermined threshold for a positive study outcome (lower limit of the 95% CI for Day 28 ORR ≥ 40%), with an ORR at Day 28 of 56.3% (95% CI: 44.0, 68.1). Responses were rapid and durable, with the majority of patients (62.0%) achieving their first response within the first 14 days of treatment, and a median DOR at 6 months of 345 days.

Safety

Overall, ruxolitinib was well tolerated by patients enrolled in the REACH2 and REACH1 trials, and its safety profile was consistent with the known pathology of post-alloSCT GvHD. Cytopenias were among the most common AEs observed and were more frequently reported in the ruxolitinib group than the BAT group. However, cytopenias are a common complication of alloSCT (9) and are known AEs of ruxolitinib. Although these events require regular blood count monitoring, they are generally reversible upon discontinuation of ruxolitinib (73). Feedback from UK clinicians has confirmed that the toxicity profile of ruxolitinib is acceptable and compares well with other treatments for SR-aGvHD (27).

Strengths and limitations of the clinical evidence base

REACH2 is a high-quality study, which was used as the basis for the successful marketing authorisation application to MHRA. The trial population was consistent with that of the licensed indication and the final scope.

While aGvHD is a rare disease (74), the pivotal REACH2 trial had a large sample size (N=309), and included UK trial sites and patients. UK clinicians further confirmed that the baseline characteristics of the patients in the REACH2 trial were consistent with those of UK patients with SR-aGvHD (9).

The ruxolitinib dose (10 mg) used in REACH2 is in line with the recommended dose, and the concomitant medications used by patients in the trial are consistent with those expected to be used in UK practice. However, clinical experts indicated that the treatments used as part of BAT within REACH2 and their distribution did not fully align with those received in UK clinical practice: it was noted there was little use of low-dose MTX or sirolimus in the UK and that the use of agents included in REACH2 varied between centres (9). Following this feedback, the UK clinical experts were asked to provide a treatment distribution which more accurately reflects UK clinical practice (65), which was used in the economic model, as discussed in Section B.3.2.4.2.

Another strength of the REACH2 trial is that HRQoL data were captured using both EQ-5D-5L and FACT-BMT questionnaires. Feedback from UK clinicians has confirmed that PRO was an important endpoint to evaluate in patients with GvHD (9).

REACH2 included an exploratory endpoint which assessed which patients required hospitalisation either in a bone marrow transplant unit, or the general ward. Median duration of hospital stay in the bone marrow transplant unit was higher in the BAT arm (42 days, IQR: 24–67) than in the ruxolitinib arm (32.5 days, IQR: 8–53). UK clinicians explained that this data is particularly relevant for patients with aGvHD (11).

Conclusion

Results from the REACH2 trial, complemented with data from the Phase 2 REACH1 trial, show that ruxolitinib offers statistically significant improvements in response rates and FFS vs standard therapies, as well as a manageable toxicity profile, and is associated with improved HRQoL. Ruxolitinib offers a convenient treatment option and demonstrates clinically meaningful benefits to patients with SR-aGvHD, who have a high unmet clinical need for an effective and well-tolerated therapy.

B.3. Cost effectiveness

Summary of cost-effectiveness

- A *de novo* cost-effectiveness model was developed to assess the cost-effectiveness of ruxolitinib compared with BAT (established clinical management without ruxolitinib) as a treatment for people aged 12 years and older with aGvHD who have inadequate response to corticosteroids, in line with the pivotal RCT REACH2
- A multi-state model (MSM) structure was used based on a review of the literature, the REACH2 trial, and clinical expert opinion. This approach was selected to capture disease progression and the natural history of the condition in an accurate way
- Utility values were derived from EQ-5D data in adults and adolescents
- Healthcare resource use and subsequent treatments were obtained from THE literature, supplemented by clinical opinion where appropriate

Cost-effectiveness results

- Owing to the severity of the disease, patients with SR-aGvHD experienced a substantial quality-adjusted life-year (QALY) shortfall compared with the general population (Section B.3.6) and therefore SR-aGvHD met the criteria for decision severity modifier in this indication
- Base-case results showed that ruxolitinib is a cost-effective treatment option for patients with aGvHD aged 12 and above who have an inadequate response to steroids, with an ICER of £33,133, reduced to £27,611 when the severity modifier is applied
- Probabilistic sensitivity analyses and deterministic sensitivity analyses were conducted, and scenario analyses demonstrated that the cost-effectiveness results were robust. The key drivers and source of uncertainty were the choice of analyses used to generate transition probabilities and the inclusion of cGvHD and the related costs in the model
- As more patients in the ruxolitinib arm (33.8%) than the BAT arm (21.9%) develop cGvHD rather than experiencing mortality, and cGvHD is associated with a high cost even before receiving any treatment, this has a substantial effect on the cost-effectiveness results. Scenarios excluding the resource use costs associated with cGvHD show improved cost-effectiveness vs the model base-case (£5,884 without the severity multiplier, and £4,903 with the severity modifier), and are considered relevant for consideration.

Summary

SR-aGvHD is a potentially debilitating condition with a high unmet need for an effective and well-tolerated treatment which can be taken orally. This analysis demonstrates that ruxolitinib is a cost-effective treatment option for patients with SR-aGvHD, and additionally allows for these immune compromised patients to receive treatment away from the hospital, alleviating NHS capacity issues in terms of IV administration of many therapies within BAT

B.3.1. Published cost-effectiveness studies

An SLR was conducted to identify economic evaluations and healthcare resource use (HCRU) & cost data on patients with aGvHD. A detailed description of the SLR methodology and search strategies is presented in Appendix G. The SLR comprised a de novo SLR performed in July 2019, a first SLR update conducted in September 2021, and a second SLR update performed in January 2024.

Overall, a total of 106 publications were included, reporting on both aGvHD and cGvHD. Of these, 54 publications were most relevant to the current decision problem, comprising 30 publications reporting on aGvHD patients alone, 18 publications reporting separate data for aGvHD and cGvHD patients, and six publications reporting on GvHD of unspecified type. A further 52 publications were included that are not relevant to the current decision problem, comprising 49 publications reporting on cGvHD patients alone, and three miscellaneous economic publications (for further details, see Appendix G).

Of the 54 publications most relevant to the current decision problem, four publications related to four unique economic evaluations and 50 publications related to 42 unique HCRU & cost studies (Section B.3.5). Since the four economic evaluations were performed from Canadian, Australian, Singaporean, and Russian perspectives, respectively, none are immediately applicable to healthcare decision-making in England and Wales. The key characteristics of the four economic evaluations are summarised in Table 18.

Table 18: Key characteristics of economic evaluations identified by the SLR

Study	Country	Summary of model	Patient population (age)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Ong 2023 (75)	Singapore	Semi-Markov model with 4 tunnel health states (week 0, 1, 2, and 3) then overall responders, non-responders, and death	Steroid-refractory aGvHD (≥12 years)	Ruxolitinib: 1.04 BAT: 0.89 Incremental QALYs: 0.15	Ruxolitinib: SGD 65,336 BAT: SGD 96,415 Incremental cost: SGD −31,079	Ruxolitinib dominant
CADTH 2022 (SR0688-000) (76)	Canada	Semi-Markov model with 4 tunnel health states (week 0, 1, 2, and 3) then overall responders, non-responders, and death	Grade II-IV steroid-refractory aGvHD (≥12 years)	Ruxolitinib: 1.07 BAT: 0.92 Incremental QALYs: 0.15	Ruxolitinib: CAN $172,207 BAT: CAN $212,141 Incremental cost: CAN $−39,934	Ruxolitinib dominant
PBAC 2022 (ruxolitinib) (77)	Australia	Microsimulation model with 3 health states: responder, non-responder, dead	Grade II-IV steroid-refractory aGvHD (≥12 years)	Ruxolitinib: 0.8430 BAT: 0.6187 Incremental QALYs: 0.2243	Ruxolitinib: redacted BAT: AUS $23,958 Incremental cost: redacted	ICER redacted, but in the range of AUS $55,000 to $65,000/QALY
Moiseev 2018 (78)	Russia	Cost-minimisation analysis	Steroid-refractory aGvHD (age NR)	NA	6-month per patient costs: Ruxolitinib for aGvHD: ₽5,160,685 Etanercept for aGvHD: ₽3,626,654	NA

₽= Rubles.

Abbreviations: aGvHD, acute graft-versus-host disease; AUS, Australian; BAT, best available therapy; CADTH, Canadian Agency for Drugs and Technologies in Health; CAN, Canadian; ICER, incremental cost-effectiveness ratio; NA, not applicable; NR, not reported; PBAC, Pharmaceutical Benefits Advisory Committee; QALY, quality-adjusted life year; SGD, Singapore dollar; SLR, systematic literature review.

B.3.2. Economic analysis

No published cost-effectiveness studies were identified that are directly applicable to the current technology appraisal, as none were performed from a UK perspective. As such, a *de novo* cost-effectiveness model was developed to assess the incremental cost-effectiveness of ruxolitinib versus established clinical management from a UK NHS and personal social services (PSS) perspective.

B.3.2.1. Patient population

In line with the REACH2 trial (50), the marketing authorisation, the decision problem, and the final scope (Sections B.1.1 and B.1.2), the cost-effectiveness analysis comprised of patients with aGvHD aged 12 years and older who have an inadequate response to corticosteroids.

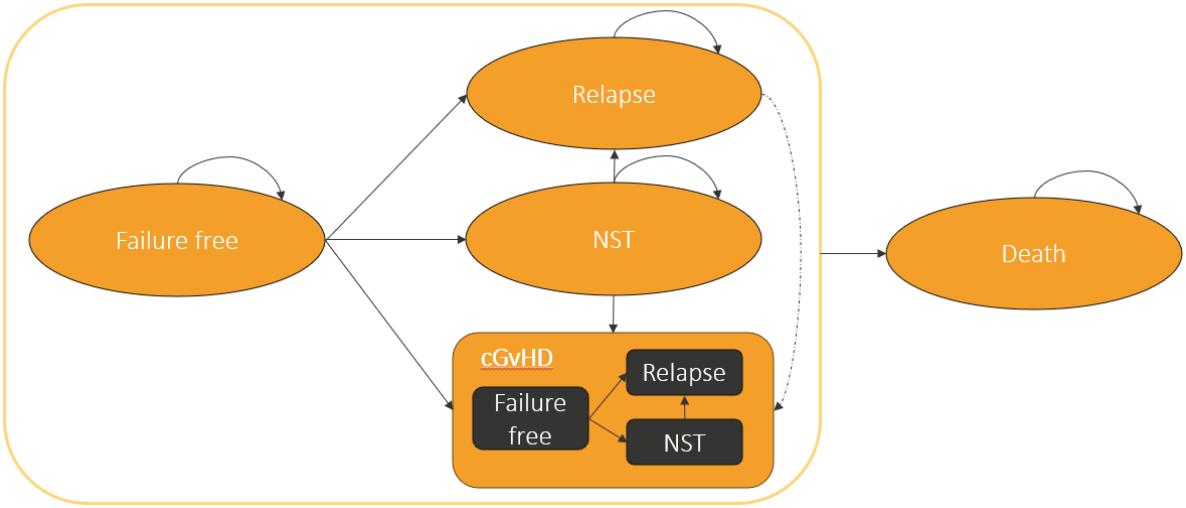
B.3.2.2. Model Structure

A *de novo* cost-effectiveness model was developed in Microsoft® Excel. The model is based around FFS and the incidence of cGvHD. It contains the following 7 mutually exclusive health states:

- Failure-free
- New systemic treatment
- Disease relapse
- cGvHD
- cGvHD requiring new systemic treatment
- Relapse following cGvHD
- Death

A schematic of the model can be seen in Figure 13.

Figure 13: Model structure



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

B.3.2.2.1. Health states and movement between health states

B.3.2.2.1.1 Acute GvHD health states

1. **Failure-free:** Steroid-refractory acute GvHD patients enter the model in the failure-free state and receive either ruxolitinib or BAT. Patients will stay in this health state until they experience treatment failure as defined in the REACH2 trial (receive a new systemic aGvHD therapy, experience a relapse of their underlying malignancy, or experience NRM). The longer a patient stays in this health state, the higher their quality of life (QoL) becomes.
2. **New systemic therapy (NST):** Patients will enter this health state from the failure-free state if they experience a non-fatal failure event that leads to being placed on new systemic aGvHD therapy. In this health state, patients will receive a third-line (3L) BAT as per investigator's judgement, and generally experience a decline in their QoL compared to the failure-free state. From here, patients can either (a) stay in this health state, (b) develop a recurrence of their underlying malignancy, (c) develop cGvHD, or (d) die.
3. **Relapse:** Patients will enter the relapse state from the failure-free state if they experience a non-fatal failure event due to the recurrence of their underlying malignancy. In this health state, patients discontinue study treatment, and can either (a) remain in this health state, (b) develop cGvHD, or (c) die.

B.3.2.2.1.2 Chronic GvHD health states

1. **cGvHD failure-free:** Patients can enter the cGvHD failure-free state from any of the aGvHD health states. Patients will stay here until they (a) experience treatment failure as defined in the REACH3 trial (receive a new systemic cGvHD therapy, experience a relapse of their underlying malignancy), or (b) die.

2. **cGvHD NST:** Patients can enter the cGvHD NST state from the cGvHD failure-free state. Patients will receive 3L cGvHD treatments which consist of adjusted distributions of BAT in REACH3 in line with clinical expert opinion, as well as belumosudil which was recently recommended by NICE as a 3L therapy for cGvHD (58). Patients will stay here until they (a) develop a recurrence of their underlying malignancy, or (b) die.

3. **cGvHD relapse:** Patients will enter the cGvHD relapse state from the cGvHD failure-free state or the cGvHD NST state if they experience a non-fatal failure event due to the recurrence of their underlying malignancy. Patients in this state are assumed to not receive any further treatment for cGvHD. Patients in this state can either (a) remain in this health state, or (b) die.

B.3.2.2.1.3 Death

Patients can enter the death state from any health state if they experience death due to any cause. This is an absorbing health state.

B.3.2.2.2. Rationale and justification for choice of model structure

The choice of health states within the model was informed by UK clinical expert opinion in both individual validation calls (9) and an advisory board (65), a review of the literature (see Section B.2.1), and data from the REACH2 and REACH3 trials to ensure the natural history of the condition is accurately reflected. The model is based on FFS, which was deemed a clinically relevant endpoint by UK clinical experts (9). FFS captures the progression of disease, including different failure mechanisms that may be associated with different health outcomes and costs. Basing the model on FFS enables clinically important differences in costs and outcomes amongst the patients who experienced the clinically distinct events within FFS to be captured appropriately.

FFS is a composite endpoint defined as the time from the date of randomisation to date of:

- Haematological disease relapse/progression
- Non-relapse mortality
- Addition of new systemic aGvHD treatment

Within the assessment of FFS, the development of cGvHD was treated as a competing risk.

As the model considers a lifetime time horizon, it is important to consider that patients with aGvHD are also at risk of developing cGvHD, with more than half of cGvHD cases occurring in patients who previously had aGvHD (79). This is a subsequent event in the clinical pathway for patients with aGvHD and so is reflected in the model. Patients are assumed not to transition from relapse to cGvHD, as if their disease relapses, treatment for a recurrent malignancy means patients are no longer immunosuppressed and will no longer be treated for cGvHD. This assumption is in line with statements from clinical experts in TA949 and has separately been validated with clinical expertise at the advisory board (65).

The three health states contained within the chronic portion of the model (failure-free, NST and relapse) are associated with costs and utilities specific to cGvHD. The cGvHD part of the model is also structured around FFS, which is in line with TA949 (56). Consideration was given to a model that used a single state to represent cGvHD, however outcomes with cGvHD can be heterogeneous, with the difference in outcomes for patients who relapse compared to those that require additional systemic treatment highlighted as a key issue in TA949. Subsequently, the additional granularity provided by modelling FFS with cGvHD was confirmed and this was validated with input from clinical experts (9).

B.3.2.2.2.1 Rationale for the choice of modelling approach

There have been no previous NICE submissions in aGvHD, and one submission (TA949) in cGvHD assessing belumosudil (56). While aGvHD and cGvHD differ in their pathophysiology (see Section B.1.3) (15, 35), there is overlap in the outcomes used to measure disease progression between the two and therefore The approach taken in TA949 was considered when choosing the model structure for this appraisal.

In TA949, a partitioned survival model (PartSA) based on FFS was used and included three health states; failure-free (FF), failure, and death. Failure-free survival was considered a relevant endpoint for the model, however time in the failure health state was based on the difference between FFS and OS, which does not account for the differences in the costs and quality-adjusted life-years (QALY) of patients who experienced the clinically distinct events

that make up FFS in the trials. This was also one of the criticisms made by the External Assessment Group (EAG), who considered that each failure event should be a separate health state (56). For this reason, a PartSA approach was not thought to accurately reflect the natural history of the condition, and was therefore not used in this appraisal.

In order to consider each failure event as a separate health state, and therefore accurately reflect the full trajectory of the condition, and to capture all costs and outcomes associated with ruxolitinib and BAT, this appraisal considers a multi-state model (MSM). It is important to note that the model can also be referred to as a cohort state-transition model (STM), as patients are passing through a series of clearly defined and mutually exclusive health states via estimated transition probabilities, and OS is estimated indirectly. The term MSM is used specifically to reflect the competing transitions being explicitly modelled and combined under a competing risk framework.

B.3.2.2.2.2 Implementation of health states over time

Due to the importance of considering patient history within the model, calculations are done in Visual Basic for Applications (VBA) for ease of implementation and faster computation. The implementation in VBA was validated and explained in B.3.13.2.

B.3.2.3. Features of the economic analysis

The key features of the economic analysis are summarised in Table 19. The model estimated the cost per QALY in line with the NICE methods guide (69). A lifetime time horizon was used to capture all the relevant costs and benefits associated with the introduction of ruxolitinib for patients with SR-aGvHD in England and Wales. As the mean starting age in REACH2 was 49.50 years old, the modelled time horizon is 50 years, which means the model continues up to the age of 100 years.

The model used a 4-week cycle length which was considered short enough to account for health events and changes in patients' health state. This cycle length also best captured the variations in dosing regimens across treatments and aligns with the data collection and reporting of the REACH2 trial. A half-cycle correction was applied using the life table method to account for uncertainty in the timing of transitions within the cycle period.

In the base case, the analysis was conducted from the perspective of the NHS and PSS in England and Wales and a discount rate of 3.5% per annum for costs and benefits was applied; both are in line with NICE's reference case (80).

While aGvHD and cGvHD differ in their pathophysiology (15, 35, 36), there is some overlap between the two (36) therefore, it was considered useful to provide a comparison between the approach taken in this submission for aGvHD and those used in TA949 for cGvHD in Table 19.

Table 19: Features of the economic analysis

Factor	**Previous evaluations**	***Current evaluation***	
	TA949, belumosudil for cGvHD	**Chosen values**	***Justification***
Model Structure	Partitioned survival	MSM	The PartSA approach cannot account for different disease trajectories after failure and this was criticised by the EAG in TA949 (56). The same issue is present in aGvHD, where outcomes will differ depending on reason for treatment failure and whether patients develop cGvHD. As such, a MSM was selected to capture differences in outcomes for the different events.
Health states	Failure-free, treatment failed, death	Failure-free, New Systemic Treatment, Relapse, cGvHD, cGvHD New Systemic Treatment, cGvHD Relapse, Death	By separating the failure state into New Systemic Treatment and Relapse states, the model is able to capture differences in outcomes for the different events. The separation of the failure health state from failure due to new systemic therapy and recurrent malignancy was a key EAG critique in TA949 (56).
Discount rate	3.5%	3.5%	In line with NICE guidance
Model cycle	4 weeks	4 weeks	Short enough to capture differences in costs or health effects between cycles and allow treatment schedules and comparators to be easily considered
Time horizon	40 years (lifetime)	Lifetime	It is considered sufficient to capture all meaningful differences between ruxolitinib and BAT over the life expectancy of patients with aGvHD.
Source of clinical efficacy and safety	Pooled ROCKstar and Phase 2a REACH3	REACH2 REACH3	REACH2 is the primary source of evidence for ruxolitinib in aGvHD and provides evidence for both ruxolitinib and BAT.

Factor	Previous evaluations	*Current evaluation*	
	TA949, belumosudil for cGvHD	**Chosen values**	***Justification***
			REACH3 provides data for generating transition probabilities for BAT in cGvHD
Treatment waning?	5 years for the OS benefit in the company base case	No	No waning was assumed as the long-term risk of events were similar between arms. A scenario analysis was conducted assuming waning after Year 3.
Source of utilities	Pooled ROCKstar and Phase 2a (HSUVs) Prior appraisals (HSUVs and AEs)	REACH2 (HSUVs) REACH3 (HSUVs) Prior appraisals (AEs)	In line with NICE reference case (80), EQ-5D-3L utilities were used in this submission, mapped from EQ-5D-5L. Utility values form prior appraisals have been considered for scenario analyses.
Source of costs	HES data, eMIT,BNF and NHS tariff	BNF for drug costs, NHS reference costs for disease management unit costs, and clinical expert opinion	In line with NICE reference case, previous appraisals, and input from clinicians.

Abbreviations: AE, adverse event; aGvHD, acute graft-versus-host-disease; BAT, best available therapy; BNF, British National Formulary; cGvHD, chronic graft-versus-host-disease; EAG, External Assessment Group; eMIT, electronic market information tool; EQ-5D-3L/5L, EuroQol five-dimension three-level/five-level; HES, hospital episode statistics; HSUV, health state utility value; MSM, multi-state model; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; Rux, ruxolitinib; TA, technology appraisal.

B.3.2.4. Intervention technology and comparators

B.3.2.4.1. Intervention

The intervention considered in this analysis is ruxolitinib with a dose of 10 mg twice daily (oral tablets). This is in line with the dosing outlined in the SmPC (28). The maximum treatment duration of ruxolitinib is approximately 2 years, as per the REACH2 trial (50), which is in line with UK clinical expert opinion during the advisory board (65), where the clinical experts were asked about their experience with ruxolitinib during the COVID-19 NHSE Rapid Commissioning Policy.

B.3.2.4.2. Comparator

The final scope states that the comparator for ruxolitinib is established clinical management without ruxolitinib, which includes but not limited to:

- ECP

- Combination therapy with mammalian target of rapamycin inhibitors (for example, sirolimus and/or MMF.

The comparator used in this submission is BAT (also referred to as established clinical management without ruxolitinib), which is in line with the NICE final scope and the pivotal REACH2 trial.

Clinical experts indicated that the treatments within BAT in REACH2 and their distribution did not fully align with those received in UK clinical practice. UK clinical experts explained that the use of ECP was under-represented and stated that methotrexate and everolimus are not used in the UK. During the advisory board, the UK clinical experts advised on the treatment distribution which more accurately reflects UK clinical practice which was used in the economic model.

Table 20 shows the treatments which make up BAT within the REACH2 trial in the first column, the actual proportion of patients who received these treatments in the REACH2 trial in the second column, and based on UK clinical expert input, an adjusted proportion of patients who receive these treatments in UK clinical practice in the third column. The proportions in the third column were informed by UK clinical experts during the advisory board. After some discussion, all experts reached a consensus on the numbers in Table 20 (please see the advisory board report for more details (65)). A final consideration was that, in REACH2, 3% of patients did not receive any treatment, therefore the proportions provided by the clinical experts were re-weighted to consider these patients. These values are shown in the final row of Table 20.

Table 20: BAT therapies in REACH2 and the economic analysis

Therapy	Proportion of REACH2 patients	Clinical expert input	Proportion used in the economic analysis
ATG	13%	0%	0%
ECP	27%	46%	45%
Etanercept	15%	15%	15%
Everolimus	1%	0%	0%
Infliximab	11%	15%	15%
Low-dose methotrexate	3%	0%	0%
MMF	17%	18%	17%
MSC	10%	5%	5%
Sirolimus	2%	1%	1%
No treatment	3%	–	3%

Abbreviations: ATG, anti-thymocyte globulin; BAT, best available therapy; ECP, extracorporeal photopheresis; MMF mycophenolate mofetil; MSC, mesenchymal stromal cells.

Due to the heterogenous nature of aGvHD and the prescription of different medicines according to manifestations and disease stage, it was considered appropriate to consider and model BAT as a basket of therapies with a single estimate of efficacy.

While the adjusted BAT distribution only affects costs, this was considered to be an appropriate assumption, as there was no randomisation within the BAT arm of REACH2, with patients receiving treatment according to the investigator's best judgement. As such, the individual BAT treatments are not directly comparable using REACH2 data, as treatment was assigned based on patient characteristics. Post-hoc analyses of the REACH2 trial showed similar effectiveness between treatments within BAT (p=0.522, Figure 14) and in particular the efficacy of ECP was comparable to other BAT treatments Figure 15).

Figure 14: FFS by BAT in REACH2

Abbreviations: ATG, anti-thymocyte globulin; BAT, best available therapy; ECP, extracorporeal photopheresis; FFS, failure-free survival; MMF mycophenolate mofetil; MSC, mesenchymal stromal cells; MTX, methotrexate.

Figure 15: FFS for ECP and other BAT treatment options

Abbreviations; BAT, best available therapy; ECP, extracorporeal photopheresis; FFS, failure-free survival; HR, hazard ratio.

B.3.3. Clinical parameters and variables

The principal source of clinical data used to inform the economic analysis is the pivotal REACH2 RCT, supplemented by REACH3 to inform outcomes following cGvHD. Table 21 summarises the clinical inputs used in this appraisal.

Table 21: Summary of clinical inputs

Input	Source	Reference to section in submission
Baseline patient characteristics		
Patient characteristics	REACH2	Section B.3.3.1
Transition probabilities		
Transition from failure-free survival (aGvHD)	REACH2	Section B.3.3.1
Transition from post-failure survival (aGvHD)	REACH2	Section B.3.3.1
Transition from cGvHD	REACH3	Section B.3.3.1

Input	Source	Reference to section in submission
Safety		
AEs	REACH2	Section B.3.3.3
Mortality		
Disease specific mortality	REACH2 REACH3	Section B.3.3.1
General population mortality	England and Wales life tables	Section B.3.3.4

Abbreviations: AE, adverse event; aGvHD, acute graft-versus-host disease; cGvHD, chronic graft-versus-host disease.

B.3.3.1. Baseline patient characteristics

Patient baseline characteristics from REACH2 (50) are shown in Table 22. Clinical experts confirmed that the populations within REACH2 and REACH3 are generalisable to UK clinical practice (9). Mean age and proportion female were used to inform estimation of background mortality and adjustment of HRQoL over time. Mean weight was used to estimate drug costs for those dosed according to weight. Body surface area (BSA) was used to estimate drug costs when appropriate.

Table 22: Baseline patient characteristics from REACH2

Characteristic	Value	SD	Use in the model
Mean age (years)	49.5	15.69	Used to inform estimation of background mortality and adjustment of HRQoL over time
Proportion female	41%	–	
Mean weight (kg)	66.87	14.41	Used to inform estimation of drug costs (those dosed according to weight)
BSA (m^2)	1.77	0.22	Used to inform estimation of drug costs (those dosed according to BSA)

Abbreviation: BSA, body surface area; HRQoL, health-related quality of life; SD, standard deviation.

B.3.3.2. Transition probabilities

B.3.3.2.1. Data sources

Transition probabilities for aGvHD and cGvHD were derived from individual patient data (IPD) from REACH2 and REACH3, respectively (50, 81). Within the cGvHD health-state,

only the BAT arm of the REACH3 trial was used to reflect the fact that ruxolitinib is not currently used in UK clinical practice in cGvHD. Additionally, with the recent positive NICE recommendation of belumosudil in 3L cGvHD, UK clinical experts were asked about their views on what proportion of patients currently receive this treatment. There was a consensus among all clinical experts at the advisory board that 35% of patients should receive belumosudil at 3L in cGvHD. Within the economic model, this was reflected as an adjustment to costs only, because belumosudil does not have an impact on OS as per EAG critique in TA949 (56).

Transition probabilities have been generated in-line with the methods described for the implementation of state transitions models in NICE DSU TSD 19 (82). For each state, individual survival analyses have been performed for each possible transition, treating any event which is not the event of interest as a censoring event, i.e. “competing” events are treated in the same way as loss to follow-up. It was necessary to estimate probabilities for 14 transitions, represented in Table 23.

As all transitions can be estimated using trial data, it was not necessary to estimate any transition probabilities from published evidence and the paper highlighted at the decision problem meeting was not required (83).

Table 23: Transition probabilities estimated for the model

To / From	Failure-free	NST	Relapse	cGvHD	cGvHD, NST	cGvHD, relapse	Death
Failure-free	✓	✓	✓	✓	×	×	✓
NST	×	✓	✓	✓	×	×	✓
Relapse	×	×	✓	×	×	×	✓
cGvHD	×	×	×	✓	✓	✓	✓
cGvHD, NST	×	×	×	×	✓	✓	✓
cGvHD, relapse	×	×	×	×	×	✓	✓
Death	×	×	×	×	×	×	✓

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

Transition probabilities only differ between arms for transitions from the failure-free health-state. Due to the specification of a lifetime horizon over which modelled costs and QALYs are required to be estimated, survival modelling was required to extrapolate outcomes beyond those observed in the REACH2 and REACH3 trials.

In REACH2, 49 patients in the BAT arm (32%) crossed over to ruxolitinib at the end of the randomised treatment period and therefore crossover adjustment was applied to OS, relapse-free survival and relapse and cGvHD-free survival. Crossover may bias estimates of post-failure outcomes and therefore estimates of time to relapse, death and cGvHD have been adjusted in patients who crossed over. The two-stage method recommended in NICE DSU 16 was used to adjust survival times for crossover (71). In all cases, the impact of crossover adjustment was minimal, with a maximum reduction on median survival of half a month.

Similarly, in REACH3 61 patients in the BAT arm (37%) crossed over and crossover adjustments were applied to OS and relapse-free survival. In both cases, the curves are identical until approximately Month 7, as crossover was not permitted in the first 24 weeks. There is a small drop off in both curves after this point, though they remain closely aligned until approximately 2 years, at which point a larger separation is observed. Median survival is not achieved in either analysis. Further details of the analyses undertaken, and outputs of survival models have been presented in Appendix O.

B.3.3.2.2. Outputs

Table 24 summarises the distribution used to model each transition.

Table 24: Summary of survival distribution used for each transition

Transition	Ruxolitinib	BAT
Failure-free to NST	Gompertz	Gompertz
Failure-free to relapse	Generalised gamma	Generalised gamma
Failure-free to cGvHD	Generalised gamma	Generalised gamma
Failure-free to death	Generalised gamma	Generalised gamma
NST to relapse	Exponential	
NST to cGvHD	Exponential	
NST to Death	Generalised gamma	
Relapse to death	Log-logistic	
cGvHD to NST	Gompertz	
cGvHD to relapse	Exponential	
cGvHD to death	Exponential	
cGvHD, NST to relapse	Exponential	
cGvHD, NST to death	Exponential	
cGvHD, Relapse to death	Log-normal	

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

B.3.3.2.2.1 Failure-free survival

Figure 16 shows the KM data of FFS from REACH2 for ruxolitinib and BAT and Figure 17 presents the KM curves for the individual transitions.

Figure 16: REACH2 – Failure-free survival for ruxolitinib and BAT

Abbreviations: BAT, best available therapy; KM, Kaplan-Meier.

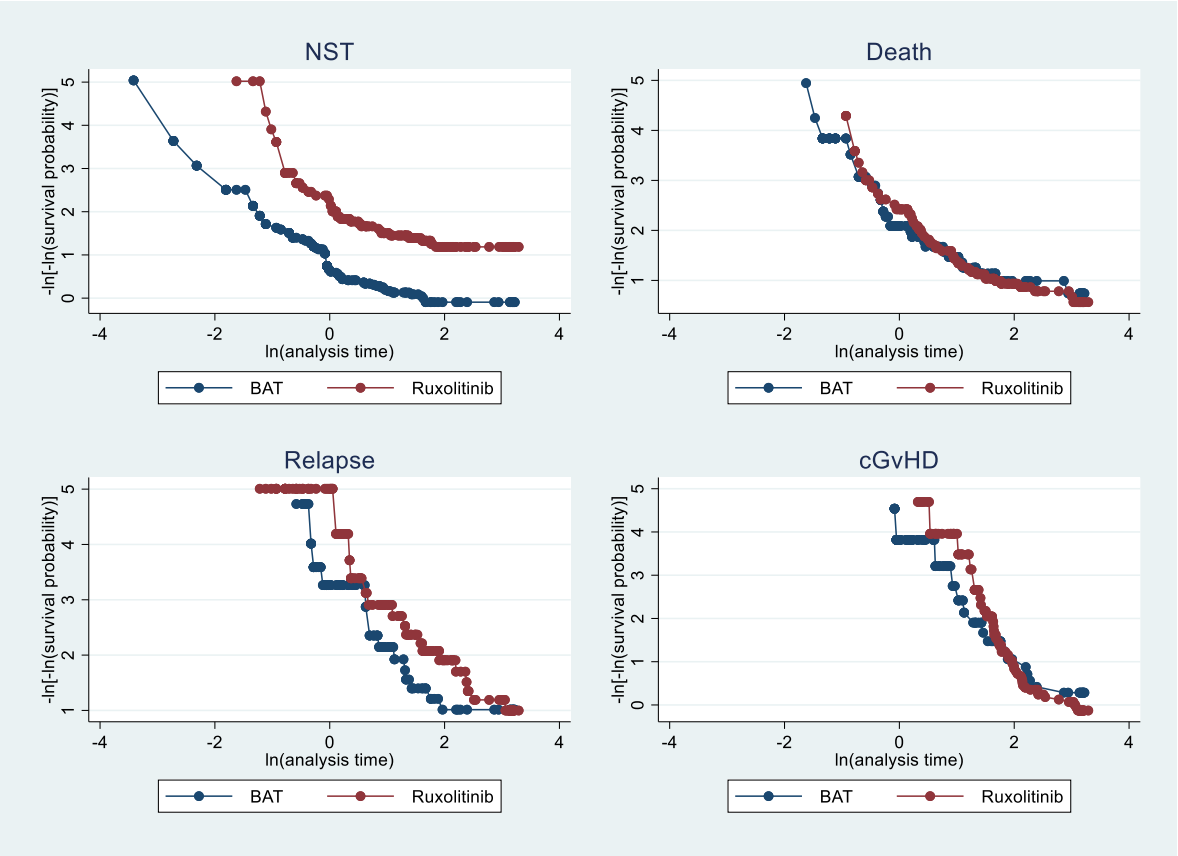
Figure 17: Kaplan-Meier data for the individual transitions in REACH2

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

Figure 18 presents the log-log survival plots for the individual transitions and shows them to be proportional over time for the NST transition, and almost identical for death. Relapse and cGvHD curves both cross, though in the case of relapse they only cross briefly and look parallel otherwise. The log-log survival plot for overall FFS shows that the curves for BAT and ruxolitinib are proportional for the majority of time, however they converge towards the end.

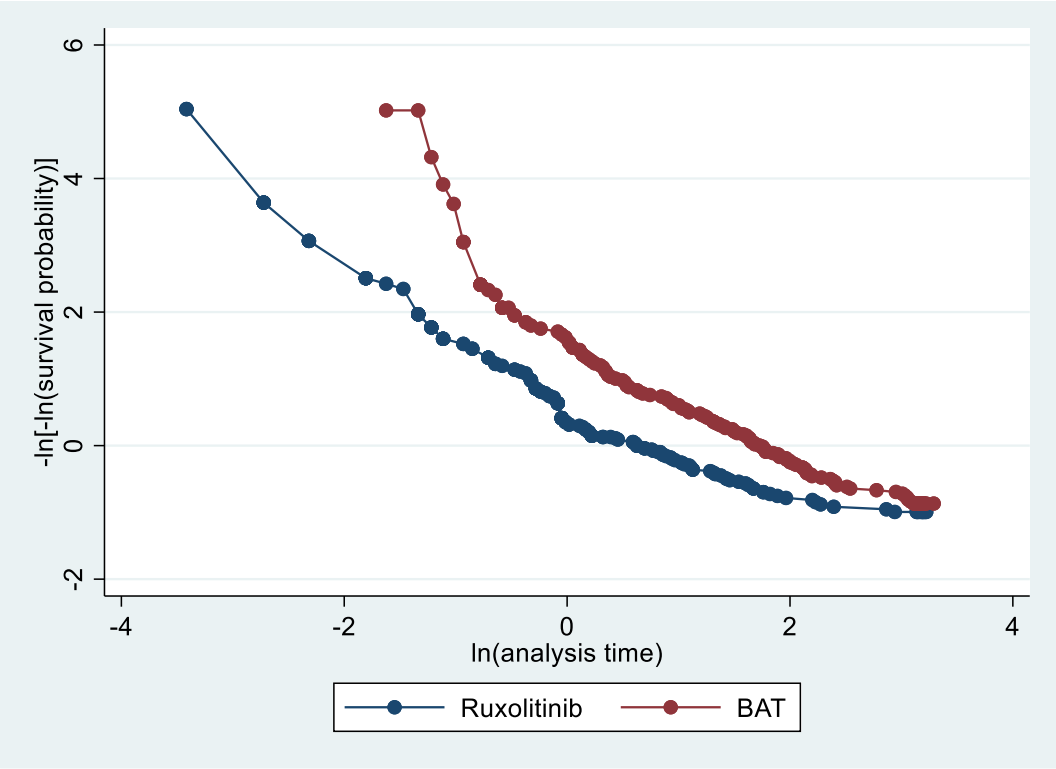
The global test does not reject the proportional hazards assumption for any individual transitions. However, this does not hold for the overall FFS curve ($p<0.01$) (Figure 19): given the log-log survival plots for the transitions cross in some cases (Figure 18), this may be down to the small number of events for some transitions.

Figure 18: Log-log survival plots for the individual transitions



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

Figure 19: Log-log survival plot for FFS



Abbreviations: BAT, best available therapy; FFS, failure-free survival.

Models were selected using a combination of statistical fit and clinical input. Akaike information criteria (AIC) and Bayesian information criteria (BIC) scores provide informative statistical tests to determine the relative fit of alternative parametric models to the observed data. Lower AIC and BIC scores indicate a better statistical fit to the observed data. For transitions from failure-free to NST, relapse and cGvHD, the KM data and fitted models for the BAT arm were presented to clinicians, with the best (statistically) fitting models highlighted. Model validation was undertaken using the individual models fit to the BAT data, as the patterns of survival for BAT with each curve are comparable between the individual and joint models, and the choice of curves is not affected by the switch to joint models.

Joint models were used for the transition from failure-free to NST as they provided a good visual fit within the observed period, and a clinically plausible long-term extrapolation. Clinical experts preferred the Gompertz model, which also showed the best statistical fit, and was therefore selected in the base case. Joint models were also used for the transition from failure-free to relapse and death, as separate individual models did not provide clinically plausible extrapolations due to the crossing of the ruxolitinib and BAT curves. As competing events are censored, it is not considered plausible to assume that the risk of failure or

relapse would be higher with ruxolitinib compared with BAT. Clinical experts preferred the generalised gamma curve for the transition from failure-free to relapse, and this was selected in the base case. For the transition from failure-free to death, the best statistically fitting model was selected, which was the generalised gamma curve.

For the transition from failure-free to cGvHD, individual models were used despite crossing to reflect the observed incidence of events within REACH2 after accounting for competing risks. The clinical experts preferred the models which showed the most slowing of failure over time, which were the Gompertz and gamma models. However, only the gamma model shows a similar shape for the ruxolitinib arm as is seen for the BAT arm, and the generalised gamma curve model shows the best statistical fit, therefore was selected for the model base case. Figure 20 presents the selected survival curves and KM data for each transition. All data on the statistical fit of the parametric survival models and comparison between KM and modelled FFS are detailed in Appendix O. Given the uncertainty in parametric extrapolation, an extensive number of scenario analyses are conducted using both individual and joint models, using curves which are clinically plausible (Section B.3.10.3).

Figure 20: KM and parametric fitting for transitions from failure-free

Abbreviations: BAT, best available therapy; cGvHD, chronic graft-versus-host-disease; KM, Kaplan-Meier; NST, new systemic therapy.

B.3.3.2.2.2 Post-failure outcomes

Figure 21 shows the KM data for each post-failure transition from REACH2 after adjustment for crossover. Curves are presented for ruxolitinib and BAT and compared to data from the pooled arms. In all cases, the difference between the ruxolitinib and BAT arms was minimal, and Cox proportion hazard models did not find a significant treatment effect for any transitions (Table 25). As such, the data from REACH2 has been pooled for post-failure transitions.

Figure 21: REACH2 – OS KM curves for ruxolitinib and BAT

Abbreviations: BAT, best available therapy; cGvHD, chronic graft-versus-host-disease; KM, Kaplan-Meier; NST, new systemic therapy; OS, overall survival.

Table 25: p-values for difference in outcomes post-failure

Transition	p-value for RUX vs BAT
NST to relapse	[redacted]
NST to cGvHD	[redacted]
NST to death	[redacted]
Relapse to death	[redacted]

Abbreviations: BAT, best available therapy; cGvHD, chronic graft-versus-host-disease; NST, new systemic therapy; RUX, ruxolitinib.

Models were selected on the basis of statistical fit, with alternative approaches using joint models and analyses without correction for crossover tested in scenario analysis. All data on the statistical fit of the parametric survival models and comparison between KM and modelled OS are detailed in Appendix O.

B.3.3.2.2.3 cGvHD

Transitions within the cGvHD state were based on data from the REACH3 trial for the BAT arm only for FFS, OS, time to relapse and time to new systemic therapy.

Figure 22, Figure 23 and Figure 24 show KM data for FFS, OS and incidence of malignancy relapse from REACH3 for BAT, respectively.

Figure 22: REACH3 – FFS KM curve for BAT

Abbreviations: BAT, best available therapy; FFS, failure-free survival; KM, Kaplan-Meier.

Figure 23: REACH3 – OS KM curve for BAT

Abbreviations: BAT, best available therapy; KM, Kaplan-Meier; OS, overall survival.

Figure 24: REACH3 – incidence of malignancy relapse KM curve for BAT

Abbreviations: BAT, best available therapy; KM, Kaplan-Meier.

The curves with the best statistical fit were selected for each transition, with the exception of the transition from relapse to death. The Gompertz curve showed the best fit here, but this gave a plateau in survival which was not deemed plausible. As such, the log-normal was selected as it had the second-best fit. All data on the statistical fit of the parametric survival models are detailed in Appendix O.

B.3.3.3. Safety

Results from REACH2 show that ruxolitinib is generally well tolerated in patients with SR-aGvHD, and the safety profile is consistent with that in myelofibrosis and polycythaemia vera. An overview of AEs that occurred in the REACH2 trial is presented in Section B.2.10.1. Grade ≥3 AEs with an incidence greater than 2% in either treatment arm of the REACH2 trial were included in the economic model. Table 26 presents the AEs from REACH2 included within the economic model.

Table 26: Adverse event incidence included in the economic model

AE	Ruxolitinib	BAT
Anaemia	35.53%	24.67%
Thrombocytopenia	33.55%	16.00%
Cytomegalovirus infection reactivation	5.92%	7.33%
Neutropenia	21.71%	12.00%
Oedema peripheral	1.97%	2.00%
Hypokalaemia	10.53%	12.00%
Pyrexia	3.29%	2.67%
Platelet count decreased	17.76%	15.33%
Nausea	0.66%	2.67%
Vomiting	2.63%	1.33%
Diarrhoea	7.24%	5.33%
Hypertension	6.58%	5.33%
White blood cell count decreased	13.16%	8.67%
Abdominal pain	2.63%	3.33%
Acute kidney injury	3.95%	4.67%
Neutrophil count decreased	11.18%	9.33%
Hypoalbuminaemia	5.92%	8.00%
Pneumonia	7.89%	8.67%
Sepsis	9.21%	11.33%
Alanine aminotransferase increased	4.61%	3.33%

AE	Ruxolitinib	BAT
Urinary tract infection	3.95%	3.33%
Hypocalcaemia	3.29%	4.00%
Hypophosphataemia	4.61%	4.67%
Hyperglycaemia	3.29%	6.00%
Blood bilirubin increased	3.29%	6.00%

Abbreviations: AE, adverse event; BAT, best available therapy.

B.3.3.4. General population mortality

Extrapolated long-term survival data should never fall below the general population mortality. Therefore, general population mortality was used as a lower bound for mortality in each health state. The England and Wales life tables (2017-2019) were used for general population mortality to exclude the impact of COVID-19 (84). The annual probabilities of death by sex and age were converted to rates of death. The rates were weighted based on the proportion of males in the model and then converted to per cycle probabilities of death by age. The model uses the sex-weighted per cycle probability of death based on the mean patient age at each cycle.

B.3.4. Measurement and valuation of health effects

Various types of utility data were used to measure and value the health effects. Health state utility values, adverse event disutilities, and aged-based utility multiplier were all used to measure and value health effects.

B.3.4.1. Health-related quality of life data from clinical trials

Health state utility values used in the analysis were estimated from REACH2 and REACH3. EQ-5D-5L responses and FACT-BMT were the tools used to collect patient-reported measures. The patient reported outcomes were administered every week during the first 2 months of the trial and every 4 weeks thereafter until the end of treatment in REACH2. In REACH3, EQ-5D-5L data was collected on Day 1 of each 28-day cycle up to Cycle 7, then every 3 cycles from Cycle 9.

B.3.4.2. Mapping

EQ-5D-3L utilities for the UK were obtained by applying the mapping function from Hernández Alava et al, 2020 (85) to EQ-5D-5L responses from REACH2 and REACH3 (50).

B.3.4.3. Health-related quality of life studies

An SLR was conducted to identify HRQoL and health state utility value (HSUV) data on patients with aGvHD or cGvHD aged ≥12 years. During title/abstract screening, publications were included that reported HSUV data and/or HRQoL data (e.g. European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core [EORTC QLQ-C30], SF-36/SF-12, FACT-BMT, FACT-G), but given the volume of HSUV evidence identified, only publications reporting HSUV data were included during full-text screening.

Overall, a total of 34 publications were included. Of these, 19 publications (related to 16 unique studies) were most relevant to the current decision problem, comprising six publications reporting on aGvHD patients alone, six publications reporting separate data for aGvHD and cGvHD patients, and seven publications reporting on GvHD of unspecified type. A further 15 publications were included that are not relevant to the current decision problem, all of which were publications reporting on cGvHD patients alone (for further details, see Appendix H).

The key characteristics of the 19 most relevant publications are summarised in Table 27. The utility values reported in each publication are presented in Appendix H and their relevance to the current decision problem and NICE reference case have also been considered in detail (Appendix H). Of the 19 relevant publications, there were only six in which GvHD was explicitly described as being both acute and steroid-refractory:

- A Canadian Agency for Drugs and Technologies in Health (CADTH) submission on ruxolitinib for the treatment of steroid-refractory aGvHD, which took utility inputs for its economic model from a previously unpublished post-hoc analysis of REACH2 (76)
- A Pharmaceutical Benefits Advisory Committee (PBAC) submission on ruxolitinib for the treatment of steroid-refractory aGvHD (and cGvHD), which took utility inputs for its economic model from a previously unpublished post-hoc analysis of REACH2 (and REACH3) (77)
- Three publications on a Phase 3 RCT of ruxolitinib for steroid-refractory aGvHD (REACH2) (86-88)
- One publication on a Phase 3 RCT of mesenchymal stromal cell (MSC) treatment for steroid-refractory aGvHD (HOVON-113-MSC) (89).

In five other publications, the population being valued was aGvHD, but was not explicitly described as steroid-refractory, while in six other publications, the population being valued was labelled as GvHD, but was not described as aGvHD or as steroid-refractory. In one of the remaining two publications, a utility value for aGvHD was estimated from proxy conditions such as hepatitis and non-infectious gastroenteritis (90) while in the other, a utility value was reported for a mixed population including 28.6% GvHD patients (91).

The EQ-5D questionnaire was used to describe health states in 11 of 19 publications. Of the remaining eight publications, five elicited utility values using the TTO method, two employed the EQ-VAS only, and one mapped utility values from HRQoL data collected with the EORTC QLQ-C30 questionnaire. Health states were valued by patients in most publications, with the exception of one publication in which the identity of participants was unclear (90) and the five TTO studies, which recruited members of the general public (92-96).

Overall, the utility data best aligned with the current decision problem and NICE reference case would be the EQ-5D-5L data for steroid-refractory aGvHD patients receiving ruxolitinib or BAT, which were collected within the REACH2 trial. This is because the EQ-5D instrument was employed, health states were valued by patients themselves, and the patient population was steroid-refractory aGvHD, including some patients from the UK. The HOVON-113-MSC trial also reported EQ-5D-5L data for steroid-refractory aGvHD patients, but the trial investigated a different intervention (MSC treatment), and no patients were from the UK.

Table 27: Key characteristics of health state utility value publications identified by the SLR

Publication	Utility instrument	Population valuing health states	GvHD type being valued	Steroid-refractory?	Study design	Intervention/ comparators (for GvHD)	Source of utility data
CADTH 2022 (SR0688-000) (76)	EQ-5D-5L	REACH2 patients (aged ≥12 years with grade II-IV SR-aGvHD)	Acute	Yes	Economic model in HTA dossier	Ruxolitinib, BAT	Data from previously unpublished post-hoc analysis of REACH2
PBAC 2022 (ruxolitinib) (77)	EQ-5D-5L	REACH2 patients (aged ≥12 years with grade II-IV SR-aGvHD)	Acute	Yes	Economic model in HTA dossier	Ruxolitinib, BAT	Data from previously unpublished post-hoc analysis of REACH2
EUDRACT 2016-002584-33 (REACH2) (88)†	EQ-5D-5L	REACH2 patients (aged ≥12 years with grade II-IV SR-aGvHD)	Acute	Yes	Interventional study (Phase 3 RCT)	Ruxolitinib, BAT	Data from study itself (REACH2)
Mohty 2021 (REACH2) (86)†	EQ-5D-5L VAS	REACH2 patients (aged ≥12 years with grade II-IV SR-aGvHD)	Acute	Yes	Interventional study (Phase 3 RCT)	Ruxolitinib, BAT	Data from study itself (REACH2)
Szer 2021 (REACH2) (87)†	EQ-5D-5L VAS	REACH2 patients (aged ≥12 years with grade II-IV SR-aGvHD)	Acute	Yes	Interventional study (Phase 3 RCT)	Ruxolitinib, BAT	Data from study itself (REACH2)
Leeneman 2023 (89)	EQ-5D-5L, EQ-5D-5L VAS	HOVON-113-MSC patients (underwent HSCT for haematological diseases and	Acute	Yes	Interventional study (Phase 3 RCT)	MSC, placebo	Data from study itself (HOVON-113-MSC)

Publication	Utility instrument	Population valuing health states	GvHD type being valued	Steroid-refractory?	Study design	Intervention/ comparators (for GvHD)	Source of utility data
		developed SR-aGvHD)					
El Jurdi 2023 (97)	EQ-5D	BMT-CTN-1101 patients (patients with leukaemia or lymphoma who underwent double umbilical cord blood or haploidentical marrow transplantation (some of which developed aGvHD)	Acute	NR	Interventional study (Phase 3 RCT)	None	Data from study itself (BMT-CTN-1101)
Hamad 2021 (46)	EQ-5D-5L, EQ-5D-5L VAS	Patients with aGvHD treated in real-world clinical practice	Acute	NR	Observational study (cross-sectional survey)	None	Data from study itself
Matza 2018 (93)‡	TTO	General population respondents in England, aged ≥18 years, valuing health states in a utility elicitation exercise	Acute	NR	Utility elicitation	None	Data from study itself

Publication	Utility instrument	Population valuing health states	GvHD type being valued	Steroid-refractory?	Study design	Intervention/ comparators (for GvHD)	Source of utility data
Matza 2020 (90)‡	TTO	General population respondents in England, aged ≥18 years, valuing health states in a utility elicitation exercise	Acute	NR	Utility elicitation	None	Data from study itself
Pidala 2009 (90)	EQ-5D	Patients who underwent allogeneic haematopoietic cell transplantation (some of which developed aGvHD)	Acute	NR	Decision analysis	None	Estimated from utility values for proxy conditions (hepatitis and non-infectious gastroenteritis) reported by Sullivan 2005 (98)
Swinburn 2015 (94)	TTO	General public in seven countries including the UK, valuing health states in a utility elicitation exercise	Acute	NR	Utility elicitation	None	Data from study itself
Castejon 2018 (95)	TTO, VAS	Adults in the UK, valuing health states in a utility elicitation exercise	NR as acute or chronic (GvHD associated with AML)	NR	Utility elicitation	None	Data from study itself

Publication	Utility instrument	Population valuing health states	GvHD type being valued	Steroid-refractory?	Study design	Intervention/ comparators (for GvHD)	Source of utility data
Dominguez-Garcia 2022 (99)	EQ-5D-5L	Patients who underwent a single alloSCT (some of which developed GvHD)	NR as acute or chronic	NR	Observational study (telephone interview/ questionnaire)	None	Data from study itself
Forsythe 2018 (100)	EQ-5D	SLR on acute myeloid leukaemia, including HSUV data for GvHD	NR as acute or chronic	NR	SLR reporting previously unpublished HSUV data	None	Mapped from EORTC QLQ-C30 data reported by Peric 2016 (101)
Johnson 2023 (91)	EQ-5D	Mixed population of patients with rare diseases, including 28.6% GvHD patients	NR as acute or chronic	NR	Observational study (cross-sectional study)	None	Data from study itself
Kurosawa 2015 (102)	EQ-5D, EQ-5D VAS	Patients who underwent allogeneic haematopoietic cell transplantation or chemotherapy for acute leukaemia (some of which developed GvHD)	NR as acute or chronic	NR	Observational study (survey)	None	Data from study itself
Kurosawa 2016 (103)	EQ-5D	Patients who underwent alloSCT for cytogenetically	NR as acute or chronic	NR	Decision analysis	None	Data from study itself

Publication	Utility instrument	Population valuing health states	GvHD type being valued	Steroid-refractory?	Study design	Intervention/ comparators (for GvHD)	Source of utility data
		intermediate-risk acute myeloid leukaemia (some of which developed GvHD)					
Nafees 2021 (96)	TTO, VAS	UK general public, valuing health states in a utility elicitation exercise	NR as acute or chronic (GvHD associated with HLH treatment)	NR	Utility elicitation	None	Data from study itself

†These three publications report data from the same unique study. ‡These two publications report data from the same unique study. Abbreviations: aGvHD, acute graft-versus-host disease; AML, acute myeloid leukaemia; alloSCT, allogeneic stem cell transplant; BAT, best available therapy; CADTH, Canadian Agency for Drugs and Technologies in Health; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D, European Quality of Life Questionnaire – 5 Dimensions; EQ-5D-5L, European Quality of Life Questionnaire – 5 Dimensions – 5 Levels; GvHD, graft-versus-host disease; HLH, haemophagocytic lymphohistiocytosis; HRQoL, health related quality of life; HSCT, haematopoietic stem cell transplantation; HSUV, health state utility value; HTA, health technology assessment; MSC, mesenchymal stromal cell; NR, not reported; RCT, randomised controlled trial; SR-aGvHD, steroid-refractory acute graft-versus-host disease; SLR, systematic literature review; TTO, time trade-off; UK, United Kingdom; VAS, visual analog scale.

B.3.4.4. Adverse reactions

Frequency of Grade 3 or higher AEs from REACH2 trial ≥ 2% were included in the model. AE disutilities and associated duration of days were taken from TA949, TA689 and TA642 (104-106) (Table 28). The QALY loss for each AE was calculated by multiplying the associated disutility with the duration of the AE. Disutility, duration per AE and QALY loss associated with each AE are presented in Table 28. A total one-off AE-related QALY loss associated with each treatment was calculated as the sum product of the disutility associated with each AE, the duration of experiencing the disutility and the rate of experiencing an AE with a given treatment. Disutility due to AEs was not considered for subsequent treatments.

Table 28: AE disutilities

AE	Mean disutility†	Duration (days)	Source
Anaemia	–0.090	23.2	TA949 (104)
Thrombocytopenia	–0.110	23.2	TA949 (104)
Cytomegalovirus infection reactivation	–0.220	14.00	TA689 (106) Infection disutility
Neutropenia	–0.160	15.09	TA689 (106)
Oedema peripheral	–0.195	18.2	Assumed to be the same as pneumonia
Hypokalaemia	0.000	0.00	TA642 (107)
Pyrexia	–0.195	18.2	Assumed to be the same as pneumonia
Platelet count decreased	–0.000	0.00	TA642 (107) Assumed no disutility for abnormal lab tests
Nausea	–0.200	3.00	Assumed to be the same as diarrhoea
Vomiting	–0.200	3.00	Assumed to be the same as diarrhoea
Diarrhoea	–0.200	3.00	TA689 (106)
Hypomagnesaemia	–0.000	0.00	TA642 (107) Assumed to be the

AE	Mean disutility†	Duration (days)	Source
			same as hypokalaemia
Hypertension	–0.020	21.0	TA949 (104)
White blood cell count decreased	–0.000	0.00	TA642 (107) Assumed no disutility for abnormal lab tests
Abdominal pain	–0.200	3.00	Assumed to be the same as diarrhoea
Acute kidney injury	–0.195	18.2	Assumed to be the same as pneumonia
Neutrophil count decreased	–0.160	15.09	TA689 (106)
Pneumonia	–0.195	18.2	TA949 (104)
Sepsis	–0.195	23.20	TA949 (104)
Alanine aminotransferase increased	–0.050	20.99	TA689 (106)
Urinary tract infection	–0.220	14.00	TA689 (106) Infection disutility
Hypocalcaemia	–0.000	0.00	Assumed to be the same as hypophosphataemia
Hypophosphataemia	–0.000	0.00	TA642 (107) Assumed no disutility for abnormal lab tests
Hyperglycaemia	–0.000	0.00	TA949 (104)
Blood bilirubin increased	–0.000	18.2	Assumed no disutility for abnormal lab tests

† Standard errors were not reported, are assumed to be 20% of the mean in the model, in line with TA949 (56).
Abbreviations: AE, adverse event; TA, technology appraisal.

B.3.4.5. Health-related quality of life data used in the cost-effectiveness model

The model used to estimate health state utility values was a mixed effects linear model for repeated measures, which was fit to all utility values obtained at baseline and all other visits where patients completed the EQ-5D questionnaire. Data for REACH2 and REACH3 were

pooled and a single model was fit to obtain estimates of utility values in each health state. Covariates included in the model were baseline utility (centred on the mean) and health state. Models were fit with and with a random intercept on the subject level.

Clinical experts highlighted that the mean utility value in REACH2 for the failure-free state was lower than they would expect for aGvHD. Utility values in REACH2 improve over time, so a link between utility and time was explored. Table 29 presents observed utility values for the failure-free health state by model cycle. Utility values improve over time, stabilising after Cycle 4. To account for this, a covariate for remaining in the failure-free health state beyond 4 cycles (112 days) was included.

Table 29: Observed utility values for failure-free patients by model cycle

Cycle	Mean EQ-5D-3L	SD	N
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]
8+	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D-3L, Euroqol five-dimension three-level; SD, standard deviation.

As EQ-5D scores were only collected for patients during the randomised treatment period, the majority of observations are in the failure-free and cGvHD health states. The EQ-5D was also collected during the crossover period, which provides data for the NST states from the crossover patients. However, there were very few observations of utility values in the relapse states, with only 16 in REACH2 and 9 in REACH3.

Table 30: Observation of EQ-5D in each health state

Health state	Observations
Failure-free	[redacted]
NST	[redacted]
Relapse	[redacted]
cGvHD	[redacted]
cGvHD, NST	[redacted]
cGvHD, relapse	[redacted]

Abbreviations: cGvHD, chronic graft-versus-host-disease; EQ-5D, EuroQol five-dimension; NST, new systemic therapy.

As there were very few observations to inform the relapse health states, analyses have been performed which does not include these patients and where the utility for relapsed disease has been taken from TA949 (0.479). This gives a total of 4 models, with and without subject-level random effects (RE) and with and without the relapse state included. Table 31 presents a comparison of the utility values included in the model and the average utility value observed for each health state.

Table 31: Utility values included in the economic model

Health state	Average health state values	Model 1: With subject level REs	Model 2: With subject level REs without relapse	Model 3: No subject level REs	**Model 4: No subject level REs, without relapse**
Failure-free, ≤4 cycles	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Failure-free, >4 cycles	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relapse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
cGvHD, failure-free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
cGvHD, NST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
cGvHD, relapse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Values in bold indicate the chosen utility values used in the economic model.
Abbreviations: cGvHD, chronic graft-versus-host-disease; NST, new systemic therapy; RE, random effect.

Clinical experts at the advisory board (65) stated that models without subject-level REs seemed more plausible, as they expected patients who remained in the failure-free state would have comparable quality of life to patients with cGvHD. They also stated that the predicted values for relapse from REACH2 and REACH3 seemed too high in comparison to other states, and their preferred analysis was Model 4. Therefore, Model 4 has been selected for the base case analysis, with other values tested via scenario analyses. Table 32 presents the outputs of the base-case utility model.

Table 32: Base case utility model

	Coefficient	**SE**	**P value**	**LCI**	**UCI**
Baseline EQ-5D-3L (centred)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health state (vs failure-free)					
NST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
cGvHD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
cGvHD, NST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>4 cycles in failure-free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Coefficient	SE	P value	LCI	UCI
Constant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: cGvHD, chronic graft-versus-host-disease; EQ-5D-3L, EuroQol five-dimension three-level; LCI, lower confidence interval; NST, new systemic therapy; SE, standard error; UCI, upper confidence interval.

A summary of all utility values used in the cost-effectiveness analysis is presented in Table 33.

Table 33: Summary of utility values used in the cost-effectiveness analysis

State	Utility value: mean (standard error)	95% CI	Reference in submission (section and page number)	Justification
Health state utilities				
Failure-free, 4 cycles	[redacted]	[redacted]	Section B.3.4.5, page 112	Based on trial data from REACH2 and REACH3 and in line with clinical opinion and previous submissions
Failure-free, >4 cycles vs FF	[redacted]	[redacted]		
NST vs FF	[redacted]	[redacted]		
Relapse	[redacted]	[redacted]		
cGvHD, failure-free, vs FF	[redacted]	[redacted]		
cGvHD, NST, vs FF	[redacted]	[redacted]		
cGvHD, relapse	[redacted]	[redacted]		

Abbreviations: cGvHD, chronic graft-versus-host-disease; CI, confidence interval; FF, failure-free; TA, technology appraisal.

B.3.4.6. Adjustment for general population utility values

In line with the NICE manual (80), utility values applied in the model were adjusted for age, using general population utility values for the UK derived from the Health Survey for England (HSE) 2014 dataset reported by Hernández Alava et al, 2022 (108). A multiplicative method was used to adjust utility values in each cycle.

B.3.5. Cost and healthcare resource use identification, measurement and valuation

An SLR was conducted to identify HCRU & cost data and economic evaluations on patients with aGvHD or cGvHD aged ≥12 years. Details of the SLR can be found in Appendix I. Of the 42 unique HCRU & cost studies, four publications reporting on four studies reported data from the UK (10, 109-111).

Firstly, Dignan 2013 (10) performed a retrospective analysis of 187 patients who underwent allogeneic transplant between January 2006 and April 2009 at the Royal Marsden NHS Foundation Trust in the UK. Overall, 118 of these patients developed GvHD; 88 had aGvHD and 58 had cGvHD (not mutually exclusive). Of the 118 patients with GvHD, 61 (52%) were steroid-refractory. The study reports multiple cost outcomes including costs of drugs, radiologic investigations, inpatient stays for transplant, inpatient stays for readmission, and total costs, in addition to HCRU outcomes such as total inpatient days. Data are stratified according to GvHD type and grade (overall GvHD [aGvHD and/or cGvHD] vs Grade I/II aGvHD vs Grade III/IV aGvHD).

Secondly, two National Institute for Health and Care Research (NIHR) Horizon Scanning Research & Intelligence Centre documents, one from 2015 and another from 2016, reported the estimated cost of ECP treatment for steroid-refractory aGvHD, which was >£30,000 over the first three months of therapy, and ≤£87,000 over the first year (109, 110). The comparators in the two publications were Remestemcel-L and begelomab, respectively, but neither document reported costs for these treatments.

Lastly, an NIHR Innovation Observatory document from 2019 reported the NHS indicative cost of ruxolitinib tablets, sourced from the British National Formulary in October 2019 (111). A pack of 56 x 5 mg tablets was priced at £1,428.00, while a pack of 56 x 10, 15, and 20 mg tablets was priced at £2,856.00.

B.3.5.1. Intervention and comparators' costs and resource use

B.3.5.1.1. Acquisition cost

Treatment acquisition costs were estimated based on treatment dosing regimens and corresponding drug prices. The dosing regimens for each treatment and the proportion of patients receiving each are provided in Table 35.

The dosing regimen for ruxolitinib was based on the dosing used in REACH2. The target dose was 10 mg twice daily, however, patients who responded to treatment could taper off ruxolitinib from Day 56, and doses could also be adjusted for safety reasons. To account for this, and to allow for other dose adjustments, the average dose in each week was calculated from REACH2 and used to assign costs. The cumulative total dose up to Day 28 and Day 56 was used to calculate the average dose in cycles 1 and 2, then the cumulative total dose over the randomised treatment period was used to calculate the average dose in subsequent cycles.

It has been assumed that patients would take whole tablets, and that wastage does not apply, therefore the average cost of ruxolitinib is each cycle is based on the total amount of ruxolitinib a patients would receive, multiplied by the cost per milligram for the 5 mg tablets. While ruxolitinib is available in 5, 10, 15 and 20 mg tablets, only the 5 and 10 mg doses were used in REACH2. Table 35 presents the dose used in the model.

Table 34: Ruxolitinib dose calculations

Period	Cumulative dose	Total dose in period	Treatment exposure in period (weeks)	Average weekly dose (mg)
Day 28	487.3	487.3	3.43	142.2
Day 56	767.5	280.2	2.40	116.6
Day 56 to end of treatment	1350.1	582.6	7.88	73.9

To calculate the cost of BAT, clinical expert input was sought on the dose of each component.

Table 35: BAT dosing assumed in the base case

Treatments	Dosing regimen	Proportion of patients
Anti-thymocyte globulin	3 mg/kg (213 mg)–7.5 mg/kg (532.5 mg) daily for 3 to 5 days	0%
Extracorporeal photopheresis	Twice weekly for 4 weeks, then every other week for 10 weeks, then every 4 weeks for up to 1 year	45%
Mesenchymal stromal cells	N/A	5%
Low-dose methotrexate	7.5 mg/m² per week	0%
Mycophenolate mofetil	1000 mg 3 times per day for 28 days	17%
Everolimus	1.5 mg daily	0%
Sirolimus	Loading dose of 6 mg, then 1–2 mg daily for 12 days	1%
Etanercept	25 mg twice weekly for 4 weeks, then 25 mg weekly for 4 weeks	15%
Infliximab	10 mg/kg per week for 4 weeks	15%
No treatment	–	3%

Abbreviations: BAT, best available therapy.

Unit costs for each treatment are provided in Table 36. Acquisition costs for all comparators are based on list prices. Drug costs were obtained from the BNF and eMIT (112, 113) and the price per session of ECP was sourced from Button et al (114), in line with TA949 (104). Drug wastage was considered in the model for infliximab. It was not possible to identify a cost for MSC (there is no list price available, and literature is unclear), and clinical experts explained that availability of MSC is uncertain and they are rarely used in the UK. Two clinical experts gave estimations of the cost (£12,000 and £20,000). For the base-case, the lower of these values has been used, and scenarios excluding MSC have been explored in scenario analysis.

Table 36: Drug acquisition costs

Treatment	Formulation size	Price per pack	Pack size	Source
Ruxolitinib	10 mg	£2,856	56 tablets	BNF (113)
Ruxolitinib ([redacted] price)	10 mg	[redacted]	56 tablets	Novartis
Anti-thymocyte globulin	250 mg	£158.77	1 vial	BNF (113)
Extracorporeal photopheresis	N/A	£1,585 per procedure	N/A	TA949 (56)
Low-dose methotrexate	2.5 mg	£3.18	100 tablets	eMIT (112)
Mycophenolate mofetil	500 mg	£9.70	100 capsules	eMIT (112)
Everolimus	2.5 mg	£536.65	30 capsules	eMIT (112)
Sirolimus	2 mg	£172.98	30 capsules	BNF (113)
Etanercept	50 mg	£357.50	4 pre-filled disposable syringes	BNF (113)
Infliximab	100 mg	£755.32	2 pre-filled disposable injection	BNF (113)
Rituximab	1400 mg/11.7ml	£1,344.65	1	BNF (113)
Mesenchymal stromal cells	–	£12,000 per treatment course	N/A	Clinical opinion (9)

Abbreviations: BNF, British National Formulary; [redacted]; N/A, not applicable; TA, technology appraisal.

The cost of concomitant steroid use has not been included in the economic model, as steroid use in REACH2 was comparable between arms and so the impact on incremental costs is expected to be minimal. This is in line with TA949 (56).

B.3.5.1.2. Treatment administration cost

Treatment administration costs have been excluded from the base case analysis. While ATG and MSC would incur a cost of administration, this is assumed to be captured in the cost of the initial hospitalisation for the BAT arm. The cost of administering ECP is assumed to be captured in the costs from Button et al (114). The remaining treatments are not anticipated to incur administration costs.

B.3.5.1.3. Duration of treatment

No patients remained on treatment at the time of the latest data cut and the duration of treatment was taken directly from REACH2. For ruxolitinib, the duration of treatment for each patient was used to calculate the proportion of patients receiving treatment in each week. The mean duration of treatment was [redacted], with a maximum duration of 678 days. All patients in the trial stopped treatment by the time the trial ended. The same approach was used for the duration of treatment with BAT, with the duration being calculated separately for each component.

Table 37: Mean treatment duration by treatment

Treatments	Mean treatment duration (days)
Ruxolitinib (oral)	[redacted]
Anti-thymocyte globulin	5.7
Extracorporeal photopheresis	61.7
Low-dose methotrexate	29.0
Mycophenolate mofetil	60.0
Everolimus	133.5
Sirolimus	25.0
Etanercept	51.0
Infliximab	37.8

B.3.5.1.4. Subsequent treatment costs

B.3.5.1.4.1 aGvHD NST health-state

Patients who enter the NST state are assumed to incur the cost of BAT, using the distribution of second line treatments from the pooled ruxolitinib and BAT arms REACH2, excluding the use of ruxolitinib. Based on UK clinical expert validation during the advisory board, duration of treatment is assumed to be equivalent to that in the failure-free health state. This was validated with clinical expert during the advisory board (65).

Table 38: Distribution of BAT therapies – aGvHD NST

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.

B.3.5.1.4.2 cGvHD

For patients with incident cGvHD, the cost of BAT has been aligned with that in REACH3, with the exception of ibrutinib and infliximab as these are not used in UK clinical practice based on UK clinical expert opinion collected during the advisory board (65). For patients who enter the NST state, it was assumed that 35% of patients receive ECP and 35% receive belumosudil. The remaining patients receiving other therapies in the same distribution as at the previous line. Table 39 summarises the cost of treatment for cGvHD, the total cost of treatment is £22,425.57 for incident cGvHD and £38,430.87 for NST cGvHD. One clinical expert considered that belumosudil usage as validated at the advisory board did not reflect the increasing use of belumosudil at 3L in cGvHD. As such, scenario analyses have been conducted with increasing proportion of belumosudil uptake to aid decision-making. A commercial arrangement is in place for belumosudil, however the details of this are not in the public domain and so the list price has been used in this analysis.

Treatment duration for cGvHD BAT was taken from REACH3 and for belumosudil the median treatment duration reported in TA949 was used.

Table 39: Cost of treatment for cGvHD

	cGvHD, treatment duration (weeks)	cGvHD, treatment dose per week	cGvHD, treatment cost	Incident cGvHD, %	CGvHD NST, %
Extracorporeal photopheresis	29.4	Twice per fortnight	£46,599.00	47.35%	35%
Mycophenolate mofetil	30.2	21,000 mg	£61.52	30.2%	57.36%
Sirolimus	39.8	7 mg	£803.61	5.99%	11.37%
Rituximab	6.4	500 mg	£3,087.89	5.17%	9.82%

	cGvHD, treatment duration (weeks)	cGvHD, treatment dose per week	cGvHD, treatment cost	Incident cGvHD, %	CGvHD NST, %
Imatinib	32.1	2800 mg	£1,565.26	6.94%	13.18%
Belumosudil (list price)	40	1400 mg	£62,613.59	0.00%	35%
Total cost				**£22,398.14**	**£38,415.25**

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

B.3.5.2. Health state unit costs and resource use

Table 40 summarises the resources that were considered by health state. For patients in the failure-free and NST states, resource use costs include hospital readmissions and outpatient visits. Monitoring costs have been excluded from the model, as they are expected to be similar between arms, in line with TA949.

The frequency of readmission has been derived from REACH2, and is assumed to be the same across the failure-free and NST states and for both arms. In REACH2, there were [redacted] unique readmissions to hospital for patients prior to relapse or death, across 267 patient-years, resulting in [redacted] hospital admissions per year, or [redacted] per 4 week cycle. The cost of a readmission has been taken from Dignan et al, identified in the SLR for HCRU (Section B.3.5). They assessed the economic burden of readmissions due to aGvHD, using 187 consecutive alloSCTs at a single centre between 2006 and 2009. They found the total cost of readmissions, including critical care, to be £28,860, with an average of 2.86 readmissions per patient, which includes the cost of inpatients stays and accounts for time spent in critical care but does not account for outpatient costs. This gives a cost per readmission of £10,091, which has been inflated to £11,786 using the Personal Social Services Research Unit (PSSRU) inflation indices. This cost was also applied for patients who initiated treatment while in hospital, which was 14.9% of patients in REACH2. Clinical expert opinion was used to inform outpatient costs for patients with aGvHD, which stated that patients with aGvHD would have outpatient visits every 1-2 weeks, and that these would stop after 3 months for failure-free patients. In the model, it has been assumed that patients in the failure-free and NST states would have 2 outpatient visits per cycle, and that these would stop after 3 cycles for the failure-free state. The cost of an outpatient visit in the model is £200.81, which is the weighted average cost of a consultant-led clinical haematology visit from the 2021/22 NHS reference costs (total outpatient attendance service code 303) (115).

Resource use in the cGvHD failure-free and NST states was taken from Avenoso et al (116), which calculates the cost of HCRU for patients with cGvHD. The found a cost of £17,339 per

patient year for inpatient admissions, £4,799 for outpatient appointments and £1,114 for critical care episodes. This gives a total cost of £23,251 per patient-year in cGvHD, or £1,782 per 4-week cycle.

The cost of recurrent malignancy was taken from TA949, which used a calculated cost of £2,719.46 per cycle based on TA642.

Table 40: Health state-related resource use costs per cycle

Health state	Cost per cycle
Initial hospitalisation	£1,754.59
Failure-free	£1,407.80 (£1,006.16 from cycle 4 on)
NST	£1,407.80
Relapse	£2,719.46
cGvHD failure-free	£1,782.44
cGvHD NST	£1,782.44
cGvHD relapse	£2,719.46

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

B.3.5.3. Adverse reaction unit costs and resource use

The cost of adverse events was taken from the literature. The AE cost for each treatment was calculated based on a per-event unit cost and the probability of experiencing AEs from REACH2 (50). The costs associated with managing AEs were derived from the PSSRU national tariff 2021/22 database (115).

Table 41 presents the AE costs used in the economic model. AE costs are applied as a one-off cost to the proportion of patients on treatment at the beginning of the model.

Table 41: AE costs

AE	Cost per event	Source
Anaemia	£410.69	TA949 (104)
Thrombocytopenia	£427.06	TA949 (104)
Cytomegalovirus infection reactivation	£1,955.82	TA689 (106)
Neutropenia	£377.81	TA689 (106)
Oedema peripheral	£576.05	Assumed to be the same as pneumonia
Hypokalaemia	£372.13	TA642 (107)
Pyrexia	£576.05	Assumed to be the same as pneumonia
Platelet count decreased	£2,055.69	TA642 (107)
Nausea	£163.36	Assumed to be the same as diarrhoea

AE	Cost per event	Source
Vomiting	£163.36	Assumed to be the same as diarrhoea
Diarrhoea	£163.36	TA689 (106)
Hypomagnesaemia	£543.55	TA642 (107)
Hypertension	£574.37	TA949 (104)
White blood cell count decreased	£163.36	TA642 (107)
Abdominal pain	£576.05	Assumed to be the same as diarrhoea
Acute kidney injury	£880.67	Assumed to be the same as pneumonia
Neutrophil count decreased	£372.13	TA689 (106)
Pneumonia	£576.05	TA949 (104)
Sepsis	£311.58	TA949 (104)
Alanine aminotransferase increased	£567.09	TA689 (106)
Urinary tract infection	£1,955.82	TA689 (106)
Hypocalcaemia	£372.13	Assumed to be the same as hypophosphataemia
Hypophosphataemia	£372.13	TA642 (107)
Hyperglycaemia	£428.03	TA949 (104)
Blood bilirubin increased	£0.00	Abnormal lab tests excluded

Abbreviations: AE, adverse event; TA, technical appraisal.

B.3.6. Severity

Table 42 and Table 43 summarise the QALY shortfall in a population of aGvHD patients aged 12 years and older who have an inadequate response to corticosteroids. Expected QALYs were generated using England and Wales lifetables (84) and general population utility values for the UK derived from the HSE 2014 dataset reported by Hernández Alava et al, 2022 (108). Patients treated with BAT would expect to receive QALYs of 1.40, an absolute shortfall of 14.46 and a proportional QALY shortfall of 0.91, meeting the criteria for a weighting of 1.2 for QALY gains.

Table 42: Summary of health state benefits and utility values for QALY shortfall analysis

State	Utility value: mean (standard error)	Undiscounted life years
Failure-free, ≤4 cycles	[redacted]	0.56
Failure-free, >4 cycles	[redacted]	
NST	[redacted]	0.27
Relapse	[redacted]	0.16
cGvHD, failure-free	[redacted]	0.59
cGvHD, NST	[redacted]	1.02
cGvHD, relapse	[redacted]	0.14

Abbreviations: cGvHD, chronic graft-versus-host-disease; NST, new systemic therapy; QALY, quality-adjusted life year.

Table 43: Summary of QALY shortfall analysis

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY shortfall
15.86	1.43	14.43	0.91

Abbreviations: QALY, quality-adjusted life year

B.3.7. Uncertainty

Acute GvHD is a rare disease and the evidence available for the currently used therapies is typically poor, as evaluations have relied on retrospective studies and small sample sizes. While the methods applied to generate comparative efficacy data for this submission are based on randomised trials and have been performed in line with best practice, the nature of the disease leads to uncertainty in the estimates.

B.3.8. Summary of base-case analysis inputs and assumptions

B.3.8.1. Summary of base-case analysis inputs

A summary of base case analysis inputs used in the model is presented in Table 44.

Table 44: Summary of model inputs applied to model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
General parameters			
Discount rate, costs	3.5%	Fixed	B.3.2.3
Discount rate, outcomes	3.5%	Fixed	
Time horizon	Lifetime	Fixed	
Baseline age	49.5	Fixed	B.3.3.1
% female	41%	Fixed	
Body weight (kg)	66.9	Fixed	
Transition probabilities			
Failure-free to NST	Gompertz	Multivariate normal distribution	B.3.3.2
Failure-free to relapse	Gamma		
Failure-free to cGvHD	Log-logistic		
Failure-free to death	Generalised gamma		

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
NST to relapse	Exponential		
NST to cGvHD	Exponential		
NST to Death	Generalised gamma		
Relapse to death	Log-logistic		
cGvHD to NST	Gompertz		
cGvHD to relapse	Exponential		
cGvHD to death	Exponential		
cGvHD, NST to relapse	Exponential		
cGvHD, NST to death	Exponential		
cGvHD, Relapse to death	Log-normal		
Background mortality			
Background mortality	England and Wales lifetables	Fixed	B.3.3.4
Utility values			
Health state utilities			
Failure-free	[redacted]	Multivariate normal distribution	B.3.4.5
NST	[redacted]		
Relapse	[redacted]	Beta distribution	
cGvHD, failure-free	[redacted]	Multivariate normal distribution	
cGvHD, NST	[redacted]		
cGvHD, relapse	[redacted]	Beta distribution	
AE disutilities			
Anaemia	–0.090	+/–20%	Table 28
Thrombocytopenia	–0.110		
Cytomegalovirus infection reactivation	–0.220		
Neutropenia	–0.160		
Oedema peripheral	–0.195		
Hypokalaemia	0.000		
Pyrexia	–0.195		
Platelet count decreased	–0.000		
Nausea	–0.200		
Vomiting	–0.200		
Diarrhoea	–0.200		
Hypomagnesaemia	–0.000		
Hypertension	–0.020		
White blood cell count decreased	–0.000		

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Abdominal pain	–0.200		
Acute kidney injury	–0.195		
Neutrophil count decreased	–0.160		
Pneumonia	–0.195		
Sepsis	–0.195		
Alanine aminotransferase increased	–0.050		
Urinary tract infection	–0.220		
Hypocalcaemia	–0.000		
Hypophosphataemia	–0.000		
Hyperglycaemia	–0.000		
Blood bilirubin increased	–0.000		
Costs			
Drug acquisition costs			
Ruxolitinib	£2856	Fixed	B.3.5.1
Anti-thymocyte globulin	£158.77		
Extracorporeal photopheresis	£1585 per procedure		
Mesenchymal stromal cells	TBC		
Low-dose methotrexate	£55.07		
Mycophenolate mofetil	£9.70		
Everolimus	£536.65		
Sirolimus	£172.98		
Etanercept	£357.50		
Pentostatin	£734.21		
Imatinib	£973.32		
Infliximab	£755.32		
Rituximab	£1344.65		
Ibrutinib	£1430.80		
Resource use costs			
Initial hospitalisation	£1,754.59	+/–20%	B.3.5.2
Failure-free, cycles 1–3	£1,407.80		
Failure-free, cycles 4+	£1,006.16		
NST	£1,407.80		
Relapse	£2,719.46		
cGvHD failure-free	£1,782.44		
cGvHD NST	£1,782.44		
cGvHD relapse	£2,719.46		

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Adverse events cost			
Anaemia	£410.69	+/–20%	B.3.5.3
Thrombocytopenia	£427.06		
Cytomegalovirus infection reactivation	£1,955.82		
Neutropenia	£377.81		
Oedema peripheral	£576.05		
Hypokalaemia	£372.13		
Pyrexia	£576.05		
Platelet count decreased	£2,055.69		
Nausea	£163.36		
Vomiting	£163.36		
Diarrhoea	£163.36		
Hypomagnesaemia	£543.55		
Hypertension	£574.37		
White blood cell count decreased	£163.36		
Abdominal pain	£576.05		
Acute kidney injury	£880.67		
Neutrophil count decreased	£372.13		
Pneumonia	£576.05		
Sepsis	£311.58		
Alanine aminotransferase increased	£567.09		
Urinary tract infection	£1,955.82		
Hypocalcaemia	£372.13		
Hypophosphataemia	£372.13		
Hyperglycaemia	£428.03		
Blood bilirubin increased	£0.00		

Abbreviations: AE, adverse event; cGvHD, chronic graft-versus-host-disease; CI, confidence interval; NST, new systemic therapy.

B.3.8.2. Assumptions

A summary of assumptions made in the model, alongside their justifications, is provided in Table 45.

Table 45: Summary of model assumptions

Assumptions	Justification	Scenario analysis
cGvHD is a relevant part of the disease pathway and should be incorporated into the model	cGvHD occurs in 30% of patients after alloSCT (56) and occurred in 28% of patients in REACH2. As such, it is considered a natural part of the disease pathway for patients with aGvHD and patients who remain alive and relapse free for longer will be more likely to experience cGvHD. Therefore, outcomes associated with cGvHD have been included in the base-case, to fully reflect the clinical pathway for aGvHD.	Scenarios without cGvHD and without the cost of cGvHD are explored. Scenarios excluding these costs are performed in line with the NICE manual (Section 4.4.16), as these costs are separate from the direct, intrinsic costs of ruxolitinib.
The REACH2 clinical trial is generalisable to UK clinical practice	Clinical experts were asked to comment on the generalisability of the BAT arm of REACH2, as well as the population included in the trial. Clinicians agreed that the trial was broadly reflective of UK clinical practice (65).	N/A
There is no difference in efficacy between BAT therapies and the efficacy of BAT does not need to be adjusted to account for the higher use of ECP in clinical practice.	Figure 14 presents FFS in REACH2 by BAT treatment and shows that FFS is broadly similar between the different treatment options. ECP is the most commonly used BAT therapy, both in REACH2 and clinical practice (as noted by UK clinical experts during the advisory board (65)), and Figure 15 compares failure-free survival with ECP to other BAT treatment options, which again shows comparable efficacy.	N/A
The proportion of patients treated with each BAT component can be informed by clinical expert opinion for costing purposes.	While there is variation in practice across the UK, inputs from the advisory board represent a mix of centres and account for this variation.	Scenarios using a higher proportion of ECP were explored, alongside a scenario using the REACH2 distribution across treatments.
Joint models with a treatment effect for ruxolitinib are suitable for extrapolating transition probabilities from the FF state	Per the global PH test, the proportional hazards assumption is not violated for any of the individual transitions, however in some cases the cumulative hazard plots do cross. By using joint models we ensure similar extrapolations shapes for each arm, which aids interpretation of the model and makes curve selection simpler.	Individual models are explored in scenario analysis.
Transition probabilities for patients who have left the failure-free state are the same for the RUX and BAT arms	After adjustment for cross-over, the KM curves for post-failure transitions show no difference between arms. Cox models found no significant treatment effect for any of these transitions	Scenarios with individual models for each arm are explored

Assumptions	Justification	Scenario analysis
	(Section B.3.3.2.2.2). This assumption is tested in scenario analysis.	
Outcomes for patients with incident cGvHD can be adequately reflected using the REACH3 trial	While REACH3 reflects outcomes for patients with SR-cGvHD, clinical experts consulted explained that SR-aGvHD patients, who go on to develop cGvHD are unlikely to respond to steroids, and therefore outcomes from REACH3 are suitable to reflect outcomes in this population. This assumption is expected to be conservative for ruxolitinib, as more patients enter the cGvHD state in the RUX arm.	N/A
Utility values increase for patients who remain in the failure-free state for 4 cycles	Clinical experts explained that the baseline utility value from REACH2 was lower than they would expect to see in aGvHD patients in the failure-free state. The utility values in REACH2 show an increase in QoL over time (Section B.3.4.5), therefore, to account for this, a covariate for remaining in the failure-free state beyond 4 cycles (112 days) was included.	Alternative utility model specifications are explored
A proportion of patients will start treatment while in hospital, and this captures the cost of treatment administration	In REACH2, 15% of patients initiated treatment while in hospital. The majority of treatment expected to incur an administration cost would be administered over a short period in an in-patient setting, such as ATG or MSC, and including additional costs risks double counting. While ECP has an on-going cost for administration, this is assumed to be captured in the cost from Button et al. (114)	Scenarios without resource use are explored
Health care resource use differs for aGvHD and cGvHD, but does not differ for patients in the FF and NST states or by treatment.	Within REACH2, the rate of readmissions and duration of readmissions was comparable between the two arms, and so no difference in readmissions between the two arms is modelled.	Scenarios without resource use are explored
For cGvHD patients who require a second treatment, a proportion will be assumed to receive BAT as per REACH3, and a proportion will receive belumosudil. This does not impact health outcomes in the BAT arm.	Belumosudil has recently become part of routine care in the UK for 3L treatment of cGvHD patients. However, while belumosudil has a positive impact on FFS, there was no observed benefit on OS, and this was reflected in the model used in TA949 (56). As patients in cGvHD arm cannot receive belumosudil until they reach the NST state (3L cGvHD), FFS is not modelled for these patients.	Scenarios without resource use and without cGvHD are explored

Abbreviations: 3L, third-line; aGvHD, acute graft-versus-host disease; ATG, anti-thymocyte globulin; BAT, best available therapy; cGvHD, chronic graft-versus-host disease; ECP, extracorporeal photopheresis; FF, failure-free; FFS, failure-free survival; KM, Kaplan-Meier; MSC, mesenchymal stromal cells; NHS, National Health Service; NST, new systemic therapy; OS, overall survival; PH, proportional hazards; QoL, quality of life; RUX, ruxolitinib; SR, steroid-refractory; TA, technology appraisal; UK, United Kingdom.

B.3.9. Base-case results

Table 46 and Table 47 present the base-case results and net health benefit, respectively. Ruxolitinib is associated with higher costs and QALYs compared to BAT. Although acquisition costs for ruxolitinib are lower than with BAT, there remains an incremental cost in the ruxolitinib arm due to life extensions, especially in the cGvHD states where to cost of medical resource utilisation (MRU) is high. Using the [redacted] price for ruxolitinib and the comparator list prices, ruxolitinib had an incremental cost-effectiveness ratio (ICER) of £33,133 compared with BAT. Once the severity modifier weighting has been applied to QALY gains, this is reduced to £27,611.

Table 46: Base-case results (deterministic), with [redacted] price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	ICER with severity modifier (£/QALY)
BAT	£79,632	2.74	1.37	–	–	–	–	–
Ruxolitinib ([redacted] price)	[redacted]	3.77	[redacted]	[redacted]	1.02	[redacted]	£33,133	£27,611

Abbreviations: BAT, best available therapy; [redacted] ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life years

Table 47: Net health benefit, with [redacted] price

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000	NHB at £20,000 with severity modifier	NHB at £30,000 with severity modifier
BAT	£79,632	1.37	–	–	–	–	–	–
Ruxolitinib ([redacted] price)	[redacted]	[redacted]	[redacted]	[redacted]	–0.38	–0.06	–0.27	0.06

Abbreviations: BAT, best available therapy; [redacted] ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALY, quality-adjusted life year.

B.3.10. Exploring uncertainty

B.3.10.1. Probabilistic sensitivity analysis

Joint parameter uncertainty was explored through probabilistic sensitivity analysis (PSA), in which all parameters are assigned distributions and varied jointly (5,000 Monte Carlo simulations were recorded). Where the covariance structure between parameters was known, correlated random draws were sampled from a multivariate normal distribution. Results were plotted on a cost-effectiveness plane (CEP) and a cost-effectiveness acceptability curve (CEAC) was generated.

PSA results (

Table 48) are congruent with the deterministic results, and ruxolitinib remains cost-effective (£26,741) at [redacted] and the comparator list prices. Figure 25 presents the CEP. The CEAC (Figure 26) 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 48: PSA results (ruxolitinib [redacted] price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	ICER with severity modifier (£/QALY)
BAT	£79,102	1.36	-	-	-	-
Ruxolitinib ([redacted] price)	[redacted]	[redacted]	[redacted]	[redacted]	£32,089	£26,741

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.

Figure 25: Cost-effectiveness plane (ruxolitinib [redacted] price, with modifier)

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

Figure 26: Cost-effectiveness acceptability curve (ruxolitinib [redacted] price, with modifier)

Abbreviations: BAT, best available therapy; [redacted]

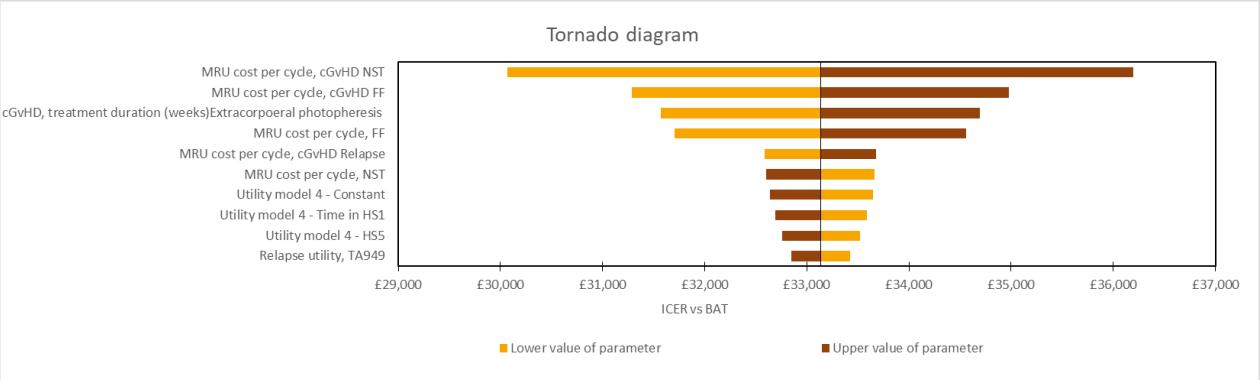
B.3.10.2. Deterministic sensitivity analysis

A one-way deterministic sensitivity analysis (DSA) was performed to investigate key drivers of the base-case results. In this analysis, input parameters were individually increased and decreased with deterministic results generated for the higher and lower values. The higher and lower values were based on 95% CIs. In the absence of such data, the higher and lower

values were calculated as ± 20% of the mean base-case value. Parameters varied in the analysis are detailed in Table 44.

Figure 27 presents the tornado diagram of ten most influential parameters on the ICER of ruxolitinib versus BAT, with outputs also described in Table 49. Results were most sensitive to the utility values used the model and the cost of MRU. Despite results being the most sensitive to these inputs, changes were modest.

Figure 27: Tornado diagram



Abbreviations: BAT, best available therapy; cGvHD, chronic graft-versus-host-disease; HS, health state; FF, failure-free; ICER, incremental cost-effectiveness ratio; MRU, medical resource use; NST, new systemic therapy; RUX, ruxolitinib; TA, technology appraisal.

Table 49: Outcomes of the DSA (with and without severity modifier)

Parameter	With severity modifier		Without severity modifier	
	ICER at lower value of parameter	ICER at upper value of parameter	ICER at lower value of parameter	ICER at upper value of parameter
MRU cost per cycle, cGvHD NST	£25,060	£30,162	£30,071	£36,194
MRU cost per cycle, cGvHD FF	£26,074	£29,147	£31,289	£34,976
cGvHD, treatment duration (weeks) ECP	£26,310	£28,911	£31,572	£34,694
MRU cost per cycle, FF	£26,422	£28,799	£31,707	£34,558
MRU cost per cycle, cGvHD Relapse	£27,156	£28,065	£32,588	£33,677
MRU cost per cycle, NST	£28,051	£27,170	£33,661	£32,605
Utility model 4 - Constant	£28,037	£27,197	£33,645	£32,636
Utility model 4 - Time in HS1	£27,989	£27,242	£33,587	£32,691
Utility model 4 - HS5	£27,932	£27,296	£33,518	£32,756
Relapse utility, TA949	£27,855	£27,371	£33,425	£32,845

Abbreviations: cGvHD, chronic graft-versus-host-disease; DSA, deterministic sensitivity analysis; ECP, extracorporeal photopheresis; FF, failure-free; HS, health state; ICER, incremental cost-effectiveness ratio; MRU, medical resource use; NST, new systemic therapy; TA, technology appraisal.

B.3.10.3. Scenario analysis

Table 50 summarises the different scenario analyses considered, with results of the scenario analyses presented in Table 51. All scenarios have been run using the [redacted] for ruxolitinib and list prices for BAT.

Table 50: Scenario analysis

Scenario	Details
Decision problem	
No discounting for costs or outcomes	To assess the impact of discounting on model outcomes
Clinical data	
Transition probabilities for the naïve analysis	Use models without adjustment for crossover (Section B.3.2.2)
Best fitting models	The choice of curves is guided AIC/BIC, rather than by clinical input (Section B.3.3.2)
Individual models for FF transitions	Separate models are fit for RUX and BAT for all transitions from the failure-free state (Section B.3.3.2). Models for transitions from FF are selected based on statistical fit and the remaining transitions are as per the base case.
Individual models, Clinician choice of curves	Aligned with the previous scenario, but with model selection informed by clinical input
Joint models for FF transitions	Joint models are fit for RUX and BAT for all transitions from the failure-free state (Section B.3.3.2). Models for transitions from FF are selected based on statistical fit and the remaining transitions are as per the base case.
Joint models, Clinician choice of curves	Aligned with the previous scenario, but with model selection informed by clinical input
Joint models for post-failure outcomes	Models including a treatment effect for RUX are fit for the post-failure states, excluding cGvHD states (Section B.3.3.2)
Treatment waning after Year 3	After Year 3, transition probabilities for ruxolitinib are set equal to BAT.
Utilities	
Average observed utility values	The average observed utility values from REACH2 and REACH3 are used for each health state
Mixed effects model	Alternative model specifications are used to generate utilities (Section B.3.4.5)
Mixed effects model, without relapse	
Fixed effects model	
cGvHD utility from TA949	cGvHD utility values taken from TA949 (56)
Costs and resource use	

Scenario	Details
ECP only for BAT	Assumes 100% of patients receive ECP as their first BAT treatment. There is no change in efficacy modelled.
BAT per clinician survey	One clinician conducted a survey of 27 transplant centres in the UK to assess the most common BAT treatments in UK clinical practice. After removing 6% the was assigned to BAT and 6.9% assigned to treatments not included in REACH2 the scenario uses the following treatment proportions: ECP, 73.7%; MMF, 9.5%; sirolimus, 4.8%; etanercept 6.6%; infliximab 3.9%; MSC, 1.5%.
ECP @ 60%	Increases the proportion of patients receiving ECP as their first-line treatment, reweighting the remaining treatment to retain the same proportional split as the model base case
ECP @ 80%	
BAT per REACH2	Using the proportion of patients receiving each treatment as was observed in REACH2
2L BAT = 1L BAT	The proportion of patients receiving each BAT treatment at 2L is equal to the proportion at 1L
No resource use costs	RUX increases survival, however the cost of providing care for patients with GvHD is high. In line with the NICE manual, a scenario is presented that removes the background costs.
cGvHD scenarios	
No costs for cGvHD	Much of the life-extension for RUX is spent in the cGvHD states, however these costs are not directly related to aGvHD and in line with the NICE manual scenarios removing these costs are considered.
No resource use for cGvHD	
BEL for 65% of 3L cGvHD	Increasing belumosudil use to 65% and assuming the remaining patients receive ECP
BEL only for 3L cGvHD	Increasing belumosudil use to 100%

Abbreviations: 1L, first-line; 2L, second-line; 3L, third-line; aGvHD, acute graft-versus-host disease; AIC, Akaike information criteria; BAT, best available therapy; BEL, belumosudil; BIC, Bayesian information criteria cGvHD, chronic graft-versus-host disease; ECP, extracorporeal photopheresis; FF, failure-free; MMF, mycophenolate mofetil; MSC, mesenchymal stromal cells; NICE, National Institute for Health and Care Excellence; RUX, ruxolitinib; TA, technology appraisal; UK, United Kingdom.

Table 51: Scenario analysis results

Scenario	Incremental costs	Incremental QALYs	ICER	ICER with severity modifier
Base-case	[redacted]	[redacted]	£33,133	£27,611
Decision problem				
Time horizon = 20 years	[redacted]	[redacted]	£43,847	£36,539
No discounting	[redacted]	[redacted]	£34,966	£29,139
Clinical data				

Scenario	Incremental costs	Incremental QALYs	ICER	ICER with severity modifier
Transition probabilities for the naïve analysis	[redacted]	[redacted]	£33,777	£28,148
Best fitting models	[redacted]	[redacted]	£32,517	£27,098
Individual models for FF transitions	[redacted]	[redacted]	£30,018	£25,015
Individual models, Clinician choice of curves	[redacted]	[redacted]	£34,039	£28,366
Joint models for FF transitions	[redacted]	[redacted]	£32,682	£27,235
Joint models, Clinician choice of curves	[redacted]	[redacted]	£31,009	£25,841
Utilities				
Average observed utility values	[redacted]	[redacted]	£31,494	£26,245
Mixed effects model	[redacted]	[redacted]	£34,743	£28,953
Mixed effects model, without relapse	[redacted]	[redacted]	£34,898	£29,081
Fixed effects model	[redacted]	[redacted]	£32,892	£27,410
cGvHD utility from TA949	[redacted]	[redacted]	£35,036	£29,197
Costs and resource use				
ECP only for BAT	[redacted]	[redacted]	£24,537	£20,448
BAT per clinician survey	[redacted]	[redacted]	£29,714	£24,762
ECP @ 60%	[redacted]	[redacted]	£30,886	£25,738
ECP @ 80%	[redacted]	[redacted]	£27,712	£23,093
BAT per REACH2	[redacted]	[redacted]	£37,028	£30,857
2L BAT = 1L BAT	[redacted]	[redacted]	£31,169	£25,974
No resource use costs	[redacted]	[redacted]	£766	£638
cGvHD scenarios				
No costs for cGvHD	[redacted]	[redacted]	Dominant	Dominant
No resource use for cGvHD	[redacted]	[redacted]	£5,884	£4,903
BEL for 65% of 3L cGvHD	[redacted]	[redacted]	£36,031	£30,025
BEL only for 3L cGvHD	[redacted]	[redacted]	£36,904	£30,753

Abbreviations: 1L, first-line; 2L, second-line; 3L, third-line; BAT, best available therapy; BEL, belumosudil; cGvHD, chronic graft-versus-host disease; ECP, extracorporeal photopheresis; FF, failure-free; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TA, technology appraisal.

B.3.10.4. Summary of sensitivity analysis

Sensitivity analyses are largely well aligned with the deterministic base-case results. Outputs of the PSA are congruent with the deterministic base-case. The DSA shows that in most scenarios, the ICER for ruxolitinib remains below £30,000 when the severity modifier is applied.

Scenario analyses show that the conclusions of the analyses are robust to a number of assumptions, with only 4 scenarios producing an ICER above £30,000 when the severity modifier is taken into account. While there is uncertainty in application of joint models for transitions from the failure-free state, the scenario analysis demonstrates that similar results are observed, regardless of the approach taken to modelling. The same is true of scenarios exploring different selections for the approach to post-failure transitions, the choice of curves and the choice utility values.

The model is sensitive to the composition of the BAT arm and clinician input has suggested that ECP is used more frequently in the UK than it was in REACH2. According to the survey of transplant centres, nearly 75% of patients are treated with ECP, and this scenario results in a reduction in the ICER to £24,762.

Resource use in GvHD is high and the model is sensitive to the resource use assumptions made in the base-case. As ruxolitinib increases survival, there are large incremental costs for resource use, and in scenarios that exclude some or all of these costs ruxolitinib becomes more cost-effective. While these scenarios are not in line with the reference case, they are recommended in the NICE manual, which states that the committee may consider scenarios with background costs removed. Scenarios excluding cGvHD, or the associated resource use, may be particularly relevant, as these costs are not directly associated with aGvHD.

B.3.11. Subgroup analysis

No subgroup analyses have been conducted.

B.3.12. Benefits not captured in the QALY calculation

Ruxolitinib is an oral therapy, and there are several benefits of oral administration to patients which have not been fully captured in the QALY calculation. Firstly, many treatments within the current BAT (namely, infliximab, ATG, MSC) require IV or blood transfusions, and it has been well documented that patients prefer less invasive methods (117). This may be a particular concern for ECP, which requires venous access and blood transfusions.

Secondly, ECP may cause significant disruption to the lives of SR-aGvHD patients due to the intense nature of the procedure; it is administered twice per week for four weeks, then every other week for ten weeks, then every four weeks for up to one year, with each procedure lasting for up to two hours. These frequent and lengthy hospital visits may be a cause of stress and anxiety for both patients and carers, and they may require time off work, which can be associated with financial loss. Time off work to receive ECP may be a particular concern considering it is only available in a few centres in England and Wales, meaning that patients must travel to receive treatment. It has also been noted during the draft scope consultation (118) and the advisory board (65) that patients are likely to need overnight stay in a local hotel, adding to their financial strain. These issues can be avoided with an oral treatment such as ruxolitinib, however these benefits are not captured in the QALY calculation.

Similarly, ruxolitinib is also likely to have additional positive benefits on workplace productivity and education compared with BAT, which is not captured in the QALY calculation.

Another important consideration is that patients with SR-aGvHD are immunocompromised and there is a benefit in keeping them away from the hospital. A key reason for the COVID-19 NHSE Rapid Commissioning Policy for ruxolitinib in aGvHD was to reduce hospital admissions and footfall during the pandemic (30). One clinical expert noted that, while this guidance is no longer in place due to the reduction in COVID-19 rates, there are times of year such as autumn and winter where SR-aGvHD patients are more susceptible to catching viruses such as respiratory syncytial virus (RSV), parainfluenza, influenza A and B and there is a benefit in being able to prescribe an oral therapy which these patients can take at home vs IV infusions. Additionally, at a time where the NHS continues to face challenging backlogs from the COVID-19 pandemic and industrial action, there is an indirect benefit of alleviating some burden on NHS staff and infrastructure which is important. Lastly, availability of an oral

treatment may have a positive effect on the QoL on carers and the family of patients with SR-aGvHD, who experience increased stress and anxiety through attending many hospital appointments, for which they will also take time off work causing financial loss to the family. These benefits are substantial but difficult to capture in the QALY calculation.

Overall, it has been highlighted by clinical experts and other healthcare professional groups that the benefits of ruxolitinib described above remain important and it should be considered that they have not been captured in the QALY (and ICER) calculation.

An important equality consideration agreed by all clinical experts during the advisory board is that ruxolitinib will answer an unmet need whereby ethnic minority patients may have less chance of developing aGvHD and thereby a higher chance of a successful transplant. When receiving a transplant, 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 (56), meaning that these patients have a higher risk of developing aGvHD and thus jeopardising their transplant outcome. Ruxolitinib, an effective treatment for SR-aGvHD, answers this unmet need. Additionally, as ECP is only available in a few centres across the UK, patients from lower socio-economic groups are less likely to receive ECP given the difficulty in/cost of travel to an ECP centre.

Another important equality consideration as highlighted by clinical experts during the individual validation teleconferences (9) was that, due to the positive experience with ruxolitinib during the COVID-19 NHSE Rapid Commissioning Policy and subsequent withdrawal of the policy, many centres and patients will use their own budgets to gain access to ruxolitinib for aGvHD. This means that there is inequality of access to ruxolitinib in aGvHD across England, and across the UK as patients in Scotland and Wales can access ruxolitinib upon request (9). Therefore, the positive recommendation of ruxolitinib will reduce the inequity of access of ruxolitinib within the UK, as well as between the UK and the rest of the world where ruxolitinib has become the standard of care (SoC) for aGvHD.

Overall, it has been highlighted by clinical experts and other healthcare professionals groups that the benefits of ruxolitinib described above remain important and it should be considered that they have not been captured in the QALY (and ICER) calculation.

B.3.13. Validation

B.3.13.1. Validation of cost-effectiveness analysis

Recognising the rarity of aGvHD, lack of previous NICE submissions within this condition, lack of SoC in the UK, and lack of updated UK clinical guidelines, UK clinical expert validation was key in ensuring the assumptions and inputs used in the analysis were relevant to UK clinical practice and therefore, outcomes predicted by the model were clinically plausible (Section B.2.2.2 and advisory board report (65)). Additionally, due to the recent experience with ruxolitinib in UK clinical practice following the COVID-19 interim guidance (30) it was especially important to collect UK clinical expert experience with ruxolitinib and validate the unmet need following termination of this guidance, as well as ensure ruxolitinib is positioned appropriately.

In total, five consultant haematologists were identified and contacted based on the following:

- Having extensive experience with stem cell transplantation and GvHD specifically,
- Having previous experience with ruxolitinib in SR-aGvHD,
- National/international speaking experience,
- Holding a faculty position within a university/teaching hospital or major research/medical/academic institution,
- Being authors of peer-reviewed articles,
- Holding a formal leadership position in a national/international medical society, and
- Previous/current clinical trial experience.

Additionally, one health economist was consulted (this is further described in Section B.3.13.2). Several experts declined to participate in the validation activities due to conflicts of interest or unavailability.

The two different forms of validation were individual validation teleconferences, and an advisory board. As these activities took place virtually during working hours, the clinicians and health economic expert were compensated as per fair market value for attending the calls and reviewing any pre-read materials.

1. **Individual validation teleconference**

Four clinical experts attended individual validation teleconferences between February and March 2024, and one expert attended a follow-up call during this time. One validation

teleconference included both a clinical and health economic expert attending together, so that both clinical and health economic concepts could be meaningfully discussed. Prior to these calls, the experts received pre-read materials in the form of a slide deck which contained the following:

- An overview of the EBMT clinical guidelines
- An overview of the REACH2 and REACH3 trials
- Efficacy and safety results
- The proposed economic modelling structure

For transparency, these materials, along with the individual teleconference reports and advisory board report are included in the reference pack of this submission. Using the information provided, clinical experts were asked to share their knowledge and view on the natural history of the condition, how UK clinical practice aligns with the latest guidelines, key unmet needs, their experience with ruxolitinib, if the populations within REACH2 and REACH3 are generalisable to the UK population and comparable with each other, if the distribution of treatments within BAT was representative of UK clinical practice, whether FFS is a relevant clinical endpoint, and their perception of the proposed economic model structure.

2. Advisory board

An advisory board was held on Wednesday, 15th May 2024 where all the clinical experts and the health economist were invited to participate. However, two declined due to unavailability, and one additional expert was contacted and agreed to participate. Therefore, the advisory board consisted of four clinical experts and one health economist. One clinical expert who was not able to attend the advisory board agreed to a follow-up call, where he was given an opportunity to add to the consensus. This was added to the advisory board report (65).

Key aspects of validation

The following key topics were discussed and validated:

- Validation of BAT treatments and their distribution in UK clinical practice,
- The dosing schedules of treatments within BAT,
- Value of FFS as a clinical endpoint,

- Appropriateness of the model structure,
- Key model inputs and assumptions,
- Plausibility of survival extrapolations and model prediction for FFS and OS,
- How ruxolitinib is used within UK clinical practice.

Clinical expert insights in both of the validation exercises were written up into a report provided along with the submission, with key feedback presented throughout the document and referenced appropriately.

B.3.13.2. Technical validation of cost-effectiveness analysis

Quality control of the economic model was performed by the model developers and by health economists not involved in the development of the model. This included cell-by-cell checks and logical checks, as well as stress testing using a predefined list of tests.

The implementation of the health state membership calculations in VBA was validated by calculating the health state membership using sheet functions for the first 5 cycles to ensure these aligned. 5 cycles was selected, as this allows for transitions into and out of every state to be tested.

B.3.14. Interpretation and conclusions of economic evidence

The base-case analysis using the [redacted] and inclusive of the severity modifier shows that ruxolitinib is a cost-effective use of NHS resources at a WTP threshold of £30,000 per QALY with an ICER of £27,611.

To assess the cost-effectiveness of ruxolitinib as a treatment for patients aged 12 and above who have an inadequate response to corticosteroids, a *de novo* cost-effectiveness analysis was conducted in line with the NICE reference case (80). The population in this appraisal aligns with the population of patients within REACH2, the final NICE scope, and the marketing authorisation granted by the MHRA in 2022 (28).

The comparator in this appraisal was BAT, in line with the NICE final scope (31). The distribution of treatments within BAT in REACH2 was adjusted to reflect UK clinical practice as advised by five UK clinical experts. Notably, a scenario is provided with a recent survey conducted by a clinician where 25/27 transplant centres in the UK described their usage of 2L therapies in aGvHD. Furthermore, the economic analysis was conducted from the perspective of the UK NHS and PSS, and can therefore be considered directly applicable to clinical practice in England and Wales.

The economic analysis was based on the pivotal REACH2 trial, which is a robust Phase 3 RCT (50). Transition probabilities and utility values for aGvHD patients were informed by the REACH2 trial, and those relating to cGvHD patients were derived from the REACH3 trial, which is another Phase 3 RCT in cGvHD patients. Both trials had UK centres and the patient populations were considered generalisable to the population of interest and comparable with each other, based on clinical expert feedback gathered as part of this appraisal (9). The efficacy and safety results of the REACH2 trial are corroborated by two RWE publications: ruxolitinib use during the COVID NHSE Rapid Commissioning Policy (30), and ruxolitinib use as part of the compassionate use policy (72). Notably, these publications emphasise the steroid-sparing effect of ruxolitinib.

As with any analysis, there are a number of limitations. Patients treated with BAT in REACH2 and REACH3 could switch to ruxolitinib, confounding the estimates of treatment effect for post-failure outcomes. The two-stage method has been applied to account for this treatment switching, however this introduces additional uncertainty into the extrapolated outcomes. Estimates of resource use were also uncertain.

It should be acknowledged that modelling GvHD as a condition is particularly challenging, as while aGvHD and cGvHD are biologically different conditions, aGvHD is the main risk factor of cGvHD therefore if an aGvHD patient is able to stay alive, there is a high chance that they will develop cGvHD in the future. This is reflected in the REACH2 trial, as up to the EOS, a total of 52 (33.8%) patients in the ruxolitinib arm developed cGvHD compared with 34 (21.9%) patients in the BAT arm. However, cGvHD is associated with a high cost for patients even before they receive any treatment. This makes the trial results difficult to interpret and is likely to affect the cost-effectiveness results. Scenarios either excluding cGvHD as a whole, or excluding the costs associated with cGvHD show improved cost-effectiveness vs the model base-case, and are considered relevant for consideration.

It should be emphasised that, in the UK, there is no established SoC for SR-aGvHD, which is accentuated by the number of treatments which are used off-label in this therapy area. The positive experience with ruxolitinib in patients with SR-aGvHD of the UK clinical experts contacted for validation purposes of this appraisal (9), who additionally explained some patients self-fund and some centres will use their own budget to gain access to ruxolitinib, along with the two RWE studies (30, 72), the BSBMTCT position statement calling for equitable access to ruxolitinib (27), and updated EBMT guidelines (26) recommending

ruxolitinib as the primary treatment option for patients with SR-aGvHD, all highlight the significant unmet need in this indication. It has been noted by the BSBMTCT in the draft scope consultation (118) that the UK is currently an outlier compared to Scotland, Wales, and the rest of the world in terms of access to innovative treatments for SR-aGvHD, as ruxolitinib is recognised as the SoC for SR-aGvHD internationally. The urgency of making ruxolitinib available in the UK was also highlighted by the BSBMTCT, Royal Marsden Hospital, and Anthony Nolan in the draft scope consultation (118).

Ruxolitinib is already recommended for patients with SR-aGvHD internationally (26, 27, 39), and the clinical experts contacted as part of this appraisal explain that a positive NICE recommendation would address the significant unmet need for an effective oral treatment in this indication. The cost-effectiveness analysis presents a strong case for ruxolitinib to be considered for routine commissioning for the treatment of SR-aGvHD in England and Wales.

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Appendices

The following appendices are provided in a standalone document:

- Appendix C: Summary of product characteristics (SmPC) and UK public assessment report
- Appendix D: Identification, selection and synthesis of clinical evidence
- Appendix E: REACH2 and REACH1 subgroup analyses
- Appendix F: REACH2 and REACH1 adverse events
- Appendix G: Published cost-effectiveness studies
- Appendix H: Health-related quality-of-life studies
- Appendix I: Cost and healthcare resource identification, measurement and valuation
- Appendix J: Clinical outcomes and disaggregated results from the model
- Appendix K: Price details of treatments included in the submission
- Appendix L: Checklist of confidential information
- Appendix M: REACH2 and REACH1 methodology – additional information
- Appendix N: REACH2 and REACH1 additional efficacy data
- Appendix O: Additional outputs of survival analysis

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 [ID6377]

Summary of Information for Patients (SIP)

June 2024

File name	Version	Contains confidential information	Date
ID6377_Ruxolitinib_SR-aGvHD_SIP_final.docx	1.0	No	19th June 2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for community organisations and community experts participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Ruxolitinib (Jakavi®)

1b) Population this treatment will be used by. Please outline the main population that is being appraised by NICE:

Patients aged 12 years and older with acute graft-versus-host-disease who have inadequate response to corticosteroids

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Ruxolitinib has a UK marketing authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA; Granted in March 2022) for the treatment of patients aged 12 years and older with acute graft versus host disease who have inadequate response to corticosteroids (https://www.medicines.org.uk/emc/product/7786/smpc)

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and community groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

The following charities have received financial support from Novartis as outlined below:

Charity Name	In-Country (£)			Cross-Border (£)		Total (£)
	2021	2022	2023	2022	2023	
Anthony Nolan	–	–	–	590	–	590
Blood Cancer UK	60,600	35,000	45,380	–	–	140,980
Leukaemia Care	50,488	525	40,000	–	377	91,389

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Acute GvHD and the impact of living with the condition

Acute graft-versus-host-disease (aGvHD) is a common complication of allogeneic stem cell transplant (alloSCT); 'allogeneic' means that the transplanted cells (the 'graft') come from a donor. AlloSCT is a potential cure for life-threatening diseases such as acute myeloid leukaemia (AML), acute lymphoblastic leukaemia (ALL) or myelodysplastic syndrome (MDS) (1, 2). Acute GvHD occurs when the graft's immune cells recognise the recipient ('host') as foreign and attack the recipient's body cells (3). It is characterised by generalised inflammation and ultimately, tissue destruction affecting multiple organs, particularly the gut, liver, lungs, bone marrow, thymus, and skin (4, 5). Typically, steroids are the first choice of treatment for aGvHD (6); patients with aGvHD that does not respond to steroid treatment (steroid-refractory acute GvHD [SR-aGvHD]) have a poor survival rate of 25% 2 years after diagnosis, decreasing further to 10% after 4 years (7, 8). In aGvHD, skin is usually the first organ affected, with a red, bumpy rash that can cover large areas of the body, and in severe cases, blistering, ulceration and skin gangrene (9-11). Gastrointestinal (GI) involvement can be severe, with bloody and voluminous diarrhoea (9, 11). Involvement of the liver may result in jaundice, painful hepatomegaly (enlargement of the liver) and fluid retention (11, 12).

As well as disease-related symptoms, patients may experience side effects from steroid treatment for aGvHD, such as high sugar levels in the blood (hyperglycaemia), high blood pressure (hypertension), insomnia, mood swings, gastritis (inflammation of the lining of the stomach), musculoskeletal disorders, impaired wound healing, and secondary adrenal insufficiency (13). Like other immunosuppressive treatments, corticosteroid use is also associated with an increased risk of infections (13, 14). Whether disease- or treatment-related, the heavy symptom burden experienced by patients with aGvHD following alloSCT significantly affects their quality of life in terms of physical and emotional well-being (15-17).

How many people live with the condition

In 2015, 1,553 people received an alloSCT in the UK, of whom 1,411 (90.85%) were in England (18). According to UK clinical experts, around 48% of alloSCT recipients will develop aGvHD, and approximately 50% of these patients will not respond to steroid treatment (6). Therefore, based on this information and on the 2022 UK data from the British Society of Blood and Marrow Transplantation and Cellular Therapy (BSBMTCT; UK total alloSCTs: 1,535; estimated England total alloSCTs: 1,535 * 0.9085 = 1,395), an estimated 670 patients will develop aGvHD in England each year, which means there are approximately 335 new cases of SR-aGvHD in England per year (19).

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

How is aGvhD diagnosed?

GvHD can be acute (aGvHD) or chronic (cGvHD). Although similar, these conditions involve distinct processes and vary in presentation (4, 5). Traditionally, aGvHD had been defined as occurring within 100 days of alloSCT, and cGvHD as arising after 100 days (4, 20) but in 2005, the National Institutes of Health issued a consensus document stating that no time limit should be set for the diagnosis of cGvHD (21). Diagnosis of aGvHD is based on clinical manifestations, specific diagnostic criteria and when available, skin, GI, or liver biopsy results (4). The three main symptoms of aGvHD are a skin rash, increased blood levels of bilirubin (a compound arising from the natural breakdown of red blood cells), and diarrhoea; a stool test is usually performed to confirm the cause of the diarrhoea (22).

Once diagnosed, aGvHD is given a grade, where 1 is mild, 2 is moderate, 3 is severe and 4 is very severe (23). Grading is based on symptoms and the number of organs involved, and is used to guide treatment and to help monitor improvements (24).

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

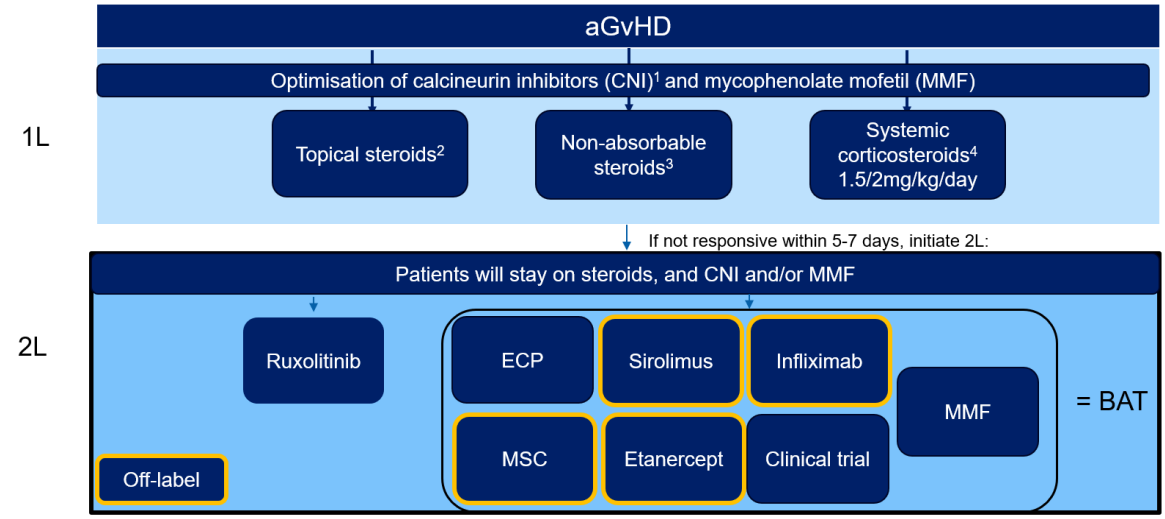
- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Patients with Grade 1 aGvHD will most frequently have skin aGvHD, for which they will receive local steroid therapy. Grade 2 and above aGvHD is typically treated with systemic steroids (steroids that work throughout the whole of the body) corticosteroids, local steroids if the patient has skin symptoms, and non-absorbable steroids (steroids that act locally and are not absorbed into the blood stream) if they have GI symptoms. In addition, patients with aGvHD are likely to receive calcineurin inhibitors (CNI) and/or mycophenolate mofetil (MMF) (6).

If a patient does not respond to treatment within 7 days, they are considered steroid-refractory. Patients with SR-aGvHD are likely to continue CNI and/or MMF in addition to systemic steroids as first-line (1L; initial treatment) therapy, however, second-line (2L; treatment given when the initial treatment has failed or stopped working) treatment options are limited. The most common 2L treatment is extracorporeal photopheresis (ECP), a procedure which destroys the blood cells which cause the GvHD, but patients need to have satisfactory blood counts, good venous access, and access to a site that offers this treatment. If ECP is not an option, clinicians will use off-label therapies such as etanercept, infliximab, mesenchymal stromal cells (MSC), and sirolimus (6).

Ruxolitinib is already recommended for the treatment of SR-aGvHD by the European Society for Blood and Marrow Transplantation (EBMT), the British Committee for Standards in Haematology (BCSH)-BSBMT, the American Society for Transplantation and Cellular Therapy (ASTCT) and the National Comprehensive Cancer Network® (NCCN®) (12, 13, 25, 26). The current treatment pathway for patients aged 12 years and above with SR-aGvHD in the UK together with the potential positioning of ruxolitinib is summarised in Figure 1.

Figure 1: Future anticipated treatment pathway for aGvHD with ruxolitinib



[1]Tacrolimus or cyclosporine. [2]Hydrocortisone, eumovate, betnovate, dermovate.[3]Budesonide or beclomethasone, to reduce dose of systemic steroids. [4]Methyl/prednisolone.
Boxes with a yellow outline represent treatments currently used off-label in the UK as informed by clinical experts.
Abbreviations: 1L, first line; 2L, second line; aGvHD, acute graft-versus-host-disease; BAT, best available therapy; CNI, calcineurin inhibitor; ECP, extracorporeal photopheresis; MMF, mycophenolate mofetil; MSC, mesenchymal stromal cells.

2d) Patient-based evidence (PBE) about living with the condition

Context:

Patient-based evidence (PBE) is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Patients with GvHD have already had to go through the challenges of alloSCT and the chemotherapy required beforehand, which have been described as “tough” and “unpleasant” (24). Once discharged from hospital they may be re-admitted with viral infections due to their weakened immune system. Patients with skin aGvHD not only experience a troublesome rash, they may also feel cold all the time. Some patients with aGvHD will go on to develop cGvHD, which affects more organs than aGvHD and requires additional treatment. The most commonly used 2L therapy for SR-aGvHD and cGvHD, ECP, is intrusive and has an intensive treatment schedule (Section 3k) with one patient describing that “the thought of having to reschedule life was daunting” (24).
A report looking at the QoL of patients with AML following alloSCT or bone marrow transplant found that 80% experienced GvHD, and that it was the second most common side effect of the transplant, immediately behind fatigue (27). Overall, side effects of transplant severely impact physical activities, work and social life for those patients.

SECTION 3: The treatment

3a) How does the new treatment work?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body.

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

How ruxolitinib works

Ruxolitinib inhibits the proteins Janus kinase 1 (JAK1) and 2 (JAK2), which initiate cell signalling triggered by cytokines, proteins that help control inflammation in the body (28). Ruxolitinib prevents the signalling of several pro-inflammatory cytokines that are involved in the development of aGvHD, therefore reducing inflammation, tissue damage, and fibrosis. Furthermore, ruxolitinib may prevent GvHD progression due to its ability to impair the production of dendritic cells, a special type of immune cell that increases immune responses (29).

How ruxolitinib is innovative

The evidence base supporting the clinical effectiveness of current treatments for SR-aGvHD is relatively poor and inconsistent (30-35). Additionally, some of these treatments fail to address the need to reduce steroid usage (36) and others such as ECP are challenging to administer. Based on clinical expert opinion, current treatment options are ineffective and lead to major side effects (6). Therefore, there is a need for a new safe and effective treatment that is convenient for patients to take and allows patients to reduce steroid usage.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

In the indication of interest to this NICE appraisal, ruxolitinib is not intended to be used as a combination therapy. However, it is expected that ruxolitinib will be used alongside other treatments used to manage symptoms and/or complications of aGvHD.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Ruxolitinib is administered orally. The recommended starting dose of ruxolitinib in aGvHD is 10 mg given orally twice daily (37). Dose reductions and temporary interruptions of treatment may be needed in patients with side-effects such as thrombocytopenia (low level of platelets, blood cells that form clots and stop or prevent bleeding), neutropenia (low level of white blood cells), or elevated total bilirubin, when those side effects do not improve after standard supportive therapy including growth factors (proteins that stimulate the bone marrow to make more blood cells), anti-infective therapies and transfusions. A one-dose level reduction step is recommended (10 mg twice daily to 5 mg twice daily or 5 mg twice daily to 5 mg once daily). In patients who are unable to tolerate ruxolitinib at a dose of 5 mg once daily, treatment should be interrupted.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

REACH2 (NCT02913261) – https://www.nejm.org/doi/10.1056/NEJMoa1917635

This was a Phase 3, randomised, open label study which compared ruxolitinib with best available therapy (BAT). Patients in the BAT arm of the study received some of the following treatments: anti-thymocyte globulin (ATG), ECP, MSCs, low-dose methotrexate (MTX), MMF, everolimus or sirolimus, etanercept, or infliximab The study included 309 patients ≥ 12 years of age with Grade 2 to 4 SR-aGvHD. It was a global multicentre study, conducted across 22 countries.

Patients were included if they:

- Were aged ≥12 years old at the time of informed consent
- Had undergone alloSCT from any donor source using bone marrow, peripheral blood stem cells (blood stem cells that can be collected straight from the blood stream – PBSCs), or cord blood (blood that remains in the placenta and in the attached umbilical cord after childbirth)
- Had clinically diagnosed Grade 2 to 4 aGvHD as per MAGIC guidelines (38)
- Had evident myeloid and platelet engraftment (i.e. the blood-forming cells received in a transplant start to grow and make healthy blood cells; engraftment must be confirmed within 48h prior to study treatment start): absolute neutrophil (white blood cell) count (ANC) >1000/mm^3 and platelets ≥20,000/mm^3. Use of growth factor supplementation and transfusion support was allowed.

Patients were excluded if they had:

- Failed prior alloSCT within the past 6 months
- Received more than one systemic treatment for SR-aGvHD
- Clinical presentation resembling de novo cGvHD or GvHD overlap syndrome
- Presented with active uncontrolled infection
- Presented with relapsed primary malignancy, or patients who were treated for relapse after the alloSCT was performed, or who may require rapid immune suppression withdrawal as pre-emergent treatment of early malignancy relapse.

REACH1 (NCT02953678) – https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7229262/

This was an open-label, single cohort Phase 2 study for ruxolitinib. The study included 71 patients ≥12 years of age with SR-aGvHD after alloSCT (Grade 2 to 4) (39, 40). It was a multicentre study conducted across the United States.

Patients were included in the study if they:

- Were aged ≥12 years old at the time of informed consent
- Had undergone first alloSCT from any donor source using bone marrow, PBSCs, or cord blood
- Had clinically suspected Grade 2 to 4 aGvHD as per MAGIC guidelines (38)
- Had evidence of myeloid engraftment (e.g., ANC ≥0.5 × 10^9/L for 3 consecutive days if ablative therapy was previously used). Use of growth factor supplementation was allowed.

Patients were excluded if they had:

- Received more than one alloSCT
- Received more than one systemic treatment in addition to corticosteroids for aGvHD
- Presence of GvHD overlap syndrome
- Presence of an active uncontrolled infection
- Evidence of relapsed primary disease or patients who have been treated for relapse after the alloSCT was performed.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition. In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a.

- Are any of the outcomes more important to patients than others and why?
- Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Efficacy evidence from REACH2

Overall response (how well a drug works against the disease)

In REACH2, ruxolitinib showed a statistically significant improvement compared with BAT in how much it worked against the disease: 62.3% of patients had responded to ruxolitinib within 28 days of starting treatment (34.4% had a complete response. i.e. their disease went away, and 27.9% a partial response, i.e. their disease got better), compared with 39.4% of patients in the BAT group (19.4% had a complete response and 20.0% a partial response).

Failure-free survival (how long patients live until their underlying disease relapses, they need to start a new treatment for aGvHD or they die from causes other than underlying disease relapse).

In REACH2, patients on ruxolitinib were alive and well for significantly longer than those on BAT (median FFS: 4.86 months in the ruxolitinib arm vs 1.02 months in the BAT arm).

Reduction of steroid treatment

In REACH2, more patients in the ruxolitinib arm (22.1%) had completely stopped steroids than in the BAT arm (14.8%) within 56 days of starting treatment. At the end of the study, there were still more patients in the ruxolitinib arm (43.5%) who had completely stopped steroids than in the BAT arm (31.6%).

Note: The REACH1 did not compare ruxolitinib with other current treatments, therefore the trial results are shown here.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as patient reported outcomes (PROs). Please include any patient preference information (PPI) relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

In REACH2, quality of life was assessed using two questionnaires, the EuroQol-five-dimension-five-level (EQ-5D-5L) and the Functional Assessment of Cancer Therapy – Bone Marrow Transplant (FACT-BMT). The EQ-5D-5L is a generic questionnaire that can be used to estimate quality of life in a range of conditions. It assesses the impact of a condition on a patient's mobility, ability to self-care, ability to undertake usual activities, pain and discomfort and anxiety and depression. The FACT-BMT questionnaire is a disease-specific questionnaire. It was designed specifically to assess the quality of life in patients undergoing bone marrow transplant.

The results found that both ruxolitinib and BAT improved quality of life, however the improvement was more pronounced with ruxolitinib than with BAT. The mean EQ-5D-5L score at the start of the trial in the ruxolitinib arm (0.51) and in the BAT arm (0.43) improved at Week 24 to 0.76 and 0.63, respectively. The mean FACT-BMT total score at the start of the trial in the ruxolitinib arm (86.04) and in the BAT arm (81.95) improved at Week 24 to 104.94 and 86.62, respectively.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer. Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Side effects occur with all drugs, however not everyone will experience them. There are side effects associated with ruxolitinib use. Based on safety data from REACH2 and REACH1 ruxolitinib is generally well tolerated by most people. Some of the most common side effects were cytopenias such as anaemia (a low number of red blood cells, due to low levels of haemoglobin), thrombocytopenia and neutropenia; however, these cytopenias were generally reversible once patients stopped treatment.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration.

Effectiveness and safety of ruxolitinib

- In REACH2, more people responded to treatment in the ruxolitinib arm (62.3%) than in the BAT arm (39.4%)
- Compared with BAT, ruxolitinib also has a statistically significant impact on FFS, which means that patients receiving ruxolitinib stay well for longer compared with those receiving BAT. In REACH2, median FFS was 4.86 months in the ruxolitinib arm vs 1.02 months in the BAT arm
- Current treatments for SR-aGvHD do not work very well and some do not help people reduce their steroid use (6, 36). Based on REACH2, ruxolitinib has demonstrated to be an effective treatment compared with BAT. People taking

ruxolitinib were also found to need less steroid therapy. By the end of REACH2, more patients were able to completely stop steroids in the ruxolitinib arm (43.5%) than in the BAT arm (31.6%)

- Ruxolitinib is an oral treatment with a recommended starting dose of 10 mg twice daily. An oral treatment provides a more convenient option for patients compared with most BAT treatments which are administered by a healthcare professional in a hospital setting. If people are receiving ruxolitinib they do not need to spend as much time travelling to appointments and receiving treatment in hospital, and reduces the overall cost burden for patients. This means that they can spend more time doing the things they enjoy such as spending time with family and friends, contributing to society through work and volunteering, and caring for their family. It also helps to protect more vulnerable people with weak immune systems, who may be exposed to infectious agents while travelling to and in hospital
- Ruxolitinib is generally well tolerated by people. The most common side effect was cytopenias, however before starting treatment blood cell counts are taken. People are normally monitored every 2–4 weeks until the dose is stabilised and cytopenias are generally reversible once patients stop treatment.

Summary
Despite their use, there is not much clinical evidence that most of the treatments currently used in the UK for SR-aGvHD are effective. Existing treatment options do not work very well and lead to major side effects. Ruxolitinib addresses a significant unmet need by offering significantly improved response rates compared with current therapies, reducing steroid usage, and is generally well tolerated with manageable side effects.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments.

One disadvantage is the possible impact of ruxolitinib on blood cell count (cytopenias), which was one the side effects noted in REACH2. However, cytopenias were generally reversible upon discontinuation of treatment. Furthermore, UK clinical experts have confirmed that they had no concerns about the side-effects of ruxolitinib, and that it compared well with other treatments (6).

3j) Value and economic considerations

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model. In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and

issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

How the model reflects the condition
The economic model has been designed to reflect the natural path of aGvHD. It is made up of three aGvHD states (failure-free survival, relapse and new systemic therapy) and similarly three cGvHD health states (failure-free survival, relapse and new systemic therapy). Although the focus is on aGvHD, it was necessary to capture the impact of cGvHD, as patients are at risk of developing cGvHD over time. Patients can die in any health state, therefore a death state has been included. All patients start in the failure-free health state and then move through the different health states based on transition probabilities, which were taken from individual patient data (IPD) observed in the REACH2 study. For cGvHD, transition probabilities were taken from the Phase 3 trial REACH3, which investigated the efficacy and safety of ruxolitinib in patients with SR-cGvHD.

Each health state is associated with specific costs and utilities. For example, patients who are failure-free have a relatively low health state cost and high quality of life (expressed by a high utility value). However, patients who relapse or move into any of the post failure-free states experience higher costs and lower utility values. The model estimates costs and benefits over a patient's lifetime in order to capture the difference in these outcomes over time between ruxolitinib and BAT.

Modelling how much a treatment extends life
Ruxolitinib extends life by keeping more patients in the failure-free health state than BAT. It should be noted that as patients on ruxolitinib live longer, a higher proportion are modelled to develop cGvHD compared with BAT.

Modelling how much a treatment improves quality of life
A higher proportion of patients receiving ruxolitinib remain in both the aGvHD and cGvHD failure-free health states compared with BAT. As the failure-free state is associated with a reasonably good utility value, more patients in the ruxolitinib treatment arm have a higher quality of life compared with BAT.

Modelling how the costs of treatment differ with the new treatment
The model captures differences in treatment costs, disease management costs, subsequent treatment costs, cGvHD costs and adverse event costs between ruxolitinib and BAT treatment arms. Treatment with ruxolitinib results in higher total costs compared with the BAT arm, mainly because patients live longer and therefore go on to incur additional disease management costs.

Uncertainty
Given that the costs and effects of both ruxolitinib and BAT are projected into the future, there is naturally some uncertainty surrounding the model results. In order to reduce uncertainty, modelled clinical and cost inputs have been varied to see how this impacts the base case results.

Cost effectiveness results
Introducing ruxolitinib into the treatment pathway would mean the NHS would incur additional costs, but also leads to improvements in patient outcomes. Based on the assumptions made by the manufacturer, ICERs were below currently accepted thresholds

for cost-effectiveness. However, it is the role of the NICE Committee to assess these assumptions, and determine if ruxolitinib is a cost-effective use of NHS resource as part of the technology appraisal process.

Additional factors
Not all benefits of treatment can be captured in the model, as outlined in Section 3k.

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations. If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Ruxolitinib is an oral therapy, and there are several benefits of oral administration to patients which have not been fully captured in the QALY calculation. Firstly, many treatments within the current BAT (namely, infliximab, ATG, ECP, MSC) require intravenous (IV) access or blood transfusions, and it has been well documented that patients prefer less invasive methods (41). Additionally, ECP may cause significant disruption to the lives of patients with SR-aGvHD due to the intense nature of the procedure; it is administered twice per week for four weeks, then every other week for ten weeks, then every four weeks for up to one year. Each procedure lasts for up to two hours. This means that patients with SR-aGvHD may need to take time off work to receive ECP, even more so considering ECP is only available in a few centres in England and Wales, meaning that patients must travel to receive treatment. An oral treatment such as ruxolitinib is likely to have additional positive benefits on workplace productivity and education compared with BAT. This is something which is not captured in the QALY calculation.

Another important consideration is that patients with SR-aGvHD are immunocompromised and there is a benefit in keeping them away from the hospital. A key reason for the Coronavirus disease 2019 (COVID-19) interim guidance for ruxolitinib in aGvHD was to reduce hospital admissions and footfall during the pandemic (42). One clinical expert noted that, while this guidance is no longer in place due to the reduction in COVID-19 rates, there are times of year such as autumn and winter where patients with SR-aGvHD are more susceptible to catching viruses such as respiratory syncytial virus (RSV), parainfluenza, influenza A and B, and there is a benefit in being able to prescribe an oral therapy which these patients can take at home vs IV infusions. Additionally, at a time where the NHS faces significant backlogs from the COVID-19 pandemic, there is an indirect but important benefit of alleviating some of the burden on NHS staff and infrastructure.

Additionally, the availability of an oral treatment may have a positive effect on the quality of life of carers and the family of patients with SR-aGvHD, who experience increased stress and anxiety through attending many hospital appointments, for which they will also take time off work, causing financial loss to the family.

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
An important equality consideration is that, 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 (43), meaning that these patients have a higher risk of developing aGvHD and thus jeopardising their transplant outcome. Regarding access to treatment, ECP is only available in a few centres across the UK, which means patients from lower socio-economic groups are less likely to receive ECP given the difficulty in/cost of travelling to an ECP centre.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
Information on ruxolitinib • REACH2 (NCT02913261) • REACH1 (NCT02953678) Information on GvHD • Anthony Nolan: https://www.anthonynolan.org/patients-and-families/recovering-a-stem-cell-transplant/graft-versus-host-disease-gvhd • Cancer Research UK: https://www.cancerresearchuk.org/about-cancer/coping/physically/gvhd • GvHD alliance: https://www.gvhdalliance.org/ • Leukemia and lymphoma society: https://www.lls.org/treatment/types-treatment/stem-cell-transplantation/graft-versus-host-disease • NHS: https://www.nhs.uk/conditions/stem-cell-transplant/risks/ Further information on NICE and the role of patients • Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE • NICE's guides and templates for patient involvement in health technology assessments Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE • EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf • National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/ • European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-

content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Absolute neutrophil count (ANC): Level of neutrophils (white blood cells) in the blood

Anaemia: A low number of healthy red bloods cells, due to low levels of haemoglobin

Biopsy: Procedure to remove a piece of tissue or a sample of cells from the body so that it can be tested in a laboratory

Bilirubin: A red-orange compound that arises from the destruction of aged or abnormal red blood cells

Clinical trial/clinical study: Research that tests how well new medical approaches work in people. They test new methods of screening, prevention, diagnosis, or treatment of a disease. They are carefully designed, reviewed, and completed, and need to be approved before they can start

Cord blood: Blood that remains in the placenta and in the attached umbilical cord after childbirth. Blood cord is rich in stem cells

Cytokine: A signalling protein that helps control inflammation in the body

Cytopenia: Low level of blood cells

Dendritic cell: A special type of immune cell that boosts immune responses

Efficacy: Measurement of a medicine's desired effect under ideal conditions, such as a clinical trial

Failure-free survival (FFS): How long patients live until their underlying disease relapses, they need to start a new treatment for aGvHD or they die from causes other than underlying disease relapse

First-line (1L) treatment: Initial treatment

Gastritis: Inflammation of the lining of the stomach

Growth factor: Protein that stimulates the bone marrow to make more blood cells

Haemoglobin: Protein found in red blood cells which carries oxygen

Hepatomegaly: Enlargement of the liver

Hyperglycaemia: High levels of sugar in the blood

Hypertension: High blood pressure

Mean: In statistics, the mean or average is the sum of numbers divided by the number of numbers. E.g. from adding the following seven numbers together and dividing by seven, the mean is 5.3: 1+3+3+6+7+8+9=37.7; 37.7/7=5.3

Median: In statistics, the median is the value separating the higher half from the lower half of a data sample that has been arranged in order, e.g. out of the following numbers, 6 is the median: 1, 3, 3, 6, 7, 8, 9

Myeloid/platelet engraftment: Engraftment occurs when the blood-forming cells received in a transplant start to grow and make healthy white blood cells (myeloid engraftment) or platelets (platelet engraftment)

Neutropenia: Low level of white blood cells

Non-absorbable steroids: Steroids that act locally in the GI tract and are not absorbed into the blood stream

Overall response rate (ORR): The total number of patients whose disease has either gone away (a complete response) or got better (a partial response)

Peripheral blood stem cells (PBSC): Blood stem cells that can be collected straight from the blood stream

Phase 3 trial/study: A clinical trial/study comparing a new treatment with the standard treatment or a placebo

Platelet: Blood cell that forms clots and stops or prevents bleeding

Quality-adjusted life year: Measure of disease burden that includes the length and quality of life

Quality of life: Measure of the overall enjoyment and happiness of life including aspects of an individual's sense of well-being and ability to carry out activities of daily living

Randomised: People allocated at random to different groups (arms) of a clinical trial

Second-line (2L) treatment: Treatment given when the initial treatment has failed, stopped working or had to be stopped because of side effects

Statistically significant: A measure of difference between groups, for example between two treatment groups. The difference is said to be statistically significant if it is greater than what might be expected to happen by chance alone

Stem cells: A special type of cell that can turn into various types of cells

Systemic treatment: Drug therapy that works throughout the whole of the body. It can be given as an injection, infusion, or oral medication

Thrombocytopenia: low level of platelets in the blood

Utility value: A value placed on the quality of life (or utility) associated with a health state. The values of utilities are measured on a scale on which 1 represents full health and 0 represents death

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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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 [ID6377]

Clarification questions

30th July 2024

File name	Version	Contains confidential information	Date
ID6377 Ruxolitinib EAG Clarification questions to PM for company [REDACTED]	**1.0**	**Yes - CiC**	**30th July 2024**

Notes for company

Highlighting in the template

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Section A: Clarification on effectiveness data

Literature searches

A 1. Please provide details of the search terms used to identify relevant data on the non-database resources searched in sections D.1.1.2.1-D1.1.2.3, G.1.1.2.1-G.1.1.2.5 and H1.1.2.1-H1.1.2.5.

Full details of the web addresses, search dates, search strategies, and keywords employed during hand-searching are now provided in the additional document **ID6377-Ruxolitinib-aGvHD_Hand-searching.**

Decision problem

A 2. Priority question. The scope and decision problem (DP) are for people aged 12 years and over, and without limiting by grade of disease. However, the eligibility criteria for the REACH trials preclude Grade I disease. Also, the baseline characteristics of the REACH trials reveal that there were no patients in REACH1 and only about 3% in REACH2 who are adolescents (under age 18). Please provide a justification for

the inclusion of adolescents and Grade I disease or exclude from the DP.

As outlined in the question, the final scope and the DP provided by NICE includes people aged 12 years and over with aGvHD who have an inadequate response to steroids. The population covered by the company submission (CS) is also in line with the MHRA licence granted in March 2022 (1).

We acknowledge that no patients in REACH1 were under the age of 18 and that approximately 3% of patients in REACH2 were under the age of 18. However, we consider that the inclusion of adolescent patients within the decision problem form appropriate based on the following reasons:

- The consideration of patients aged ≥12 years is in line with the inclusion criteria for both the REACH1 and REACH2 clinical studies and the low number of patients under the age of 18 reflects the low incidence in this age group (a view which is supported by clinical opinion)
- In line with clinical expert opinion (2), the manifestation of aGvHD between adolescent and adult patients is the same, and there are no differences in pathophysiology of aGvHD between adults and adolescents, therefore it would be clinically inappropriate to exclude adolescents from the DP. Incidence of aGvHD in adolescents is similar to that reported in adults (3), and aGvHD continues to be a major cause of morbidity and mortality after alloSCT for patients of all ages (4), representing a significant unmet medical need not only for adult patients but also adolescents
- Standard treatment for aGvHD does not differ between adolescents and adults.

In terms of patients with Grade I disease, we acknowledge that these patients were precluded from the REACH1 and REACH2 clinical studies. Clinical experts (2) have conveyed the need for an option to use ruxolitinib in patients with Grade I disease, particularly as these patients are likely to experience progression to Grade ≥II disease; it is important to consider that missing the window for optimal treatment may have negative consequences further down the line and therefore the use of

ruxolitinib in this population may be important and should be included in the DP, as per the MHRA licence and final scope.

A 3. Priority question. The CS states that, based on feedback from UK clinical experts, "If ECP is not an option, UK clinical experts will use off-label therapies such as etanercept, infliximab, mesenchymal stromal cells (MSC), and sirolimus." (p. 26) This implies that if ECP is an option then that would be the treatment of choice. The criteria that are listed for ECP to be an option are that a patient is haematologically stable, has good venous access, and has access to a site that offers this treatment.

a) Please clarify if this means that there are effectively two subgroups, one with patients who are haematologically stable with good venous access, and the other who are either not haematologically stable or have poor venous access?

We apologise for the lack of clarity surrounding the statement above within the CS. In line with clinical expert opinion, haematological stability and quality of venous access does not lead to two clinically distinct patient subgroups in UK clinical practice (2). Beyond these two factors, there are a multitude of factors which determine the treatment a patient should receive. The CS highlighted these two factors as examples of the broader set of considerations made by clinicians when deciding to offer treatment with ECP, as mentioned during the validation calls: importantly, they were not the only considerations. The clinical experts are also not aware of any available clinical outcome data in haematologically stable patients with good venous access vs those who are either not haematologically stable or have poor venous access. Further, neither we nor the clinical experts we have consulted agree that such an analysis is appropriate, and we do not have the data to conduct analyses on such subgroup.

b) Please provide an estimate of the percentage of the total acute Graft-versus-host-disease (aGvHD) population who would be in each of these subgroups.

As noted in A3 a), in line with clinical expert opinion, we do not consider these to be subgroups which are representative of clinical practice in the UK.

c) **Please clarify that for those who are haematologically stable and have good venous access, the only reason to not administer ECP and instead prescribe another treatment is lack of access to a site that offers ECP. What percentage of patients do not have access to ECP?**

Please refer to question A3a. With regards to the second part of the question neither the clinical experts, nor we, are aware of any available datasets outlining the percentage of patients who do not have access to ECP within England or Wales.

d) **Please provide clinical effectiveness and cost effectiveness analyses for two separate comparisons:**

i. **Between ruxolitinib and ECP, on the assumption that these results would be applicable those who are haematologically stable and have good venous access.**

Please refer to question A3a. Additionally, this analysis would break randomisation and introduce bias and further uncertainty. Therefore, this analysis has not been provided.

ii. **Between ruxolitinib and a comparator formed by all other types of established clinical management (ECM), on the assumption that these results would be applicable to those who are not haematologically stable or have poor venous access.**

Please refer to response in question A3d i).

Systematic review

A 4. Priority question: REACH3 was omitted from the clinical effectiveness section of the CS. However, several parameters in the CEA are estimated from its data.

a) **Please include a full description of REACH3 in Section 3, including baseline characteristics and all outcomes.**

In line with the DP and the final scope as provided by NICE, the focus of the submission is on patients with aGvHD who have an inadequate response to corticosteroids. REACH2 was therefore described in detail within the clinical section of the CS and used as the primary data source in the economic model for clinical effectiveness and safety outcomes for both ruxolitinib and BAT. However, to accurately model the disease trajectory of aGvHD, it was necessary to capture cGvHD within the economic model as a subsequent event, despite the cGvHD population being outside the population of interest in this appraisal. REACH3 was therefore used to estimate clinical effectiveness (transition probabilities) for patients who develop cGvHD when treated with BAT as ruxolitinib is not part of routine practice.

For completeness, the REACH3 primary analysis CSR (5) is provided as part of the new reference pack. Please see Table 1 (Table 10-4, page 67 from REACH3 primary analysis CSR) for patient baseline characteristics.

Table 1: Demographics and baseline characteristics – REACH3, Full analysis set

Demographic variable	RUX N=165	BAT N=164	All Patients N=329
Age (years)			
n	165	164	329
Mean (SD)	45.9 (15.68)	47.2 (16.17)	46.5 (15.92)
Median	49.0	50.0	49.0
Q1–Q3	[redacted]	[redacted]	[redacted]
Min – Max	13.0–73.0	12.0–76.0	12.0–76.0
Age category – n (%)			
Adolescents, 12 – <18 years	4 (2.4)	8 (4.9)	12 (3.6)
18 – 65 years	143 (86.7)	134 (81.7)	277 (84.2)
>65 years	18 (10.9)	22 (13.4)	40 (12.2)
Sex –n (%)			
Female	56 (33.9)	72 (43.9)	128 (38.9)
Male	109 (66.1)	92 (56.1)	201 (61.1)
Race –n (%)			
White	116 (70.3)	132 (80.5)	248 (75.4)
Black or African American	2 (1.2)	0	2 (0.6)
Asian	33 (20.0)	21 (12.8)	54 (16.4)
American Indian or Alaska Native	2 (1.2)	0	2 (0.6)

Demographic variable	RUX N=165	BAT N=164	All Patients N=329
Other	9 (5.5)	4 (2.4)	13 (4.0)
Unknown	3 (1.8)	7 (4.3)	10 (3.0)
Ethnicity –n (%)			
Hispanic/Latino	[redacted]	[redacted]	[redacted]
Not Hispanic/Latino	[redacted]	[redacted]	[redacted]
Not Reported	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Weight (kg)			
n	165	163	328
Mean (SD)	68.5 (18.29)	67.9 (16.71)	68.2 (17.50)
Median	[redacted]	[redacted]	[redacted]
Q1–Q3	[redacted]	[redacted]	[redacted]
Min – Max	32.0–128.0	37.0–128.5	32.0–128.5
Height (cm)			
n	143	150	293
Mean (SD)	169.7 (9.77)	169.4 (10.05)	169.6 (9.90)
Median	[redacted]	[redacted]	[redacted]
Q1–Q3	[redacted]	[redacted]	[redacted]
Min – Max	145.0–191.0	144.3–196.0	144.3–196.0
Body mass index (kg/m^2)			
n	143	150	293
Mean (SD)	23.4 (5.35)	23.5 (4.92)	23.4 (5.13)
Median	[redacted]	[redacted]	[redacted]
Q1–Q3	[redacted]	[redacted]	[redacted]
Min – Max	13.0–38.7	14.7–42.9	13.0–42.9
Assessment of performance status – n (%)			
ECOG	[redacted]	[redacted]	[redacted]
Karnofsky	[redacted]	[redacted]	[redacted]
Lansky	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
ECOG performance status – n (%)			
0	39 (23.6)	42 (25.6)	81 (24.6)
1	92 (55.8)	82 (50.0)	174 (52.9)
2	22 (13.3)	22 (13.4)	44 (13.4)
3	0	2 (1.2)	2 (0.6)
Missing	12 (7.3)	16 (9.8)	28 (8.5)
Karnofsky performance status – n (%)			
≥ 90	[redacted]	[redacted]	[redacted]
70 – 80	[redacted]	[redacted]	[redacted]

Demographic variable	RUX N=165	BAT N=164	All Patients N=329
50 – 60	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Lansky performance status – n (%)			
≥ 90	[redacted]	[redacted]	[redacted]
70 – 80	[redacted]	[redacted]	[redacted]
50 – 60	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]

Abbreviations: aGvHD, acute graft-versus-host-disease; BAT, best available therapy; cGvHD, chronic graft-versus-host-disease; CNI, calcineurin inhibitor; CSR, clinical study report; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; min, minimum; max, maximum; NR, not reported; Q, quartile; SD, standard deviation.

Please see Sections 11.1 of the REACH3 primary and final analysis CSRs (5, 6) for the full efficacy results of the primary and key secondary endpoints, a summary of which is presented here:

- The study met the primary and both key secondary objectives showing superiority of ruxolitinib compared with BAT for ORR, FFS, and modified Lee Symptom Scale (mLSS): response of the total symptom score (TSS) of the mLSS (at Cycle 7 Day 1)

- The superiority of ORR in the ruxolitinib arm was established in the interim analysis (ORR: 50.5% [95%CI: 40.2, 60.8] in the ruxolitinib arm and 26.3% [95%CI: 17.9, 36.1] in the BAT arm; p=0.0003) and maintained in the primary analysis (ORR: 49.7% [95%CI: 41.8, 57.6] in the ruxolitinib arm and 25.6% [95%CI: 19.1, 33.0] in the BAT arm; p<0.0001)

- After crossover treatment period, ORR at Cycle 7 Day 1 for ruxolitinib was [redacted] (95% CI: [redacted]) and similar in line with the ORR observed at Cycle 7 Day 1 during primary analysis and interim analysis

- Final analysis of FFS based on data collected from 329 subjects showed the 3-month and 6-month FFS probability was [redacted]% (95% CI: [redacted]) and [redacted]% (95% CI: [redacted]) for ruxolitinib and [redacted]% (95% CI: [redacted]) and [redacted]% (95% CI: [redacted]) for BAT, respectively

- The rate of responders based on the mLSS (as per improvement ≥ 7 points of TSS from baseline) showed a statistically significant difference between the treatment arms with p=0.0011. The odds ratio was 2.62 (95% CI: 1.42; 4.82). The response rate was 24.2% (95% CI: 17.9, 31.5) in the ruxolitinib group and 11.0% (95% CI: 6.6, 16.8) in the BAT arm.

b) Please clarify the difference between the prognosis of those patients with cGvHD who originally had aGvHD and those who developed cGvHD without experiencing aGvHD. Do this with reference to the proportions in each of the mild forms of cGvHD.

Please see answer to Q B 1. a) for a discussion on survival in patients with cGvHD, by previous aGvHD status.

c) Please compare patients in the UK who develop cGvHD after experiencing aGvHD with those in REACH3. Do this with reference to the proportions in each of the mild forms of cGvHD.

Patient baseline characteristics for REACH3, including data on the number of patients who developed cGvHD after experiencing aGvHD, are available from Table 10-6 in the REACH3 primary analysis CSR, shown here in Table 2. In REACH3, 54.7% of patients with cGvHD had a previous history of aGvHD. Please see the REACH3 primary analysis CSR for full details on the cGvHD patient population. UK clinical experts have explained that the population within REACH3 are comparable to the patients they would typically see in UK clinical practice, who develop cGvHD after experiencing aGvHD. With regards to the second part of the question, the inclusion criteria for REACH3 included patients with moderate and severe cGvHD.

Table 2: GvHD history – REACH3, FAS

Disease history	Ruxolitinib N=165	BAT N=164	All Patients N=329
Prior aGvHD – n (%)			
Any	92 (55.8)	88 (53.7)	180 (54.7)
Grade I	25 (15.2)	30 (18.3)	55 (16.7)
Grade II	53 (32.1)	43 (26.2)	96 (29.2)
Grade III	14 (8.5)	12 (7.3)	26 (7.9)
Grade IV	0	3 (1.8)	3 (0.9)

Disease history	Ruxolitinib N=165	BAT N=164	All Patients N=329
Steroid-refractory aGvHD	18 (10.9)	17 (10.4)	35 (10.6)
Time from aGvHD diagnosis to resolution (days)			
n	90	83	173
Mean (SD)	143.12 (241.795)	105.78 (173.747)	125.21 (212.118)
Median	63.50	50.00	52.00
Min–Max	4.0–1675.0	5.0–1227.0	4.0–1675.0
Time from aGvHD diagnosis to randomisation (days)			
n	92	87	179
Mean (SD)	578.76 (485.490)	631.05 (1110.281)	604.17 (846.623)
Median	454.00	370.00	416.00
Min–Max	110.0–2558.0	57.0–9981.0	57.0–9981.0
Overall severity of cGvHD at initial diagnosis			
Mild	33 (20.0)	41 (25.0)	74 (22.5)
Moderate	77 (46.7)	77 (47.0)	154 (46.8)
Severe	53 (32.1)	45 (27.4)	98 (29.8)
Unknown	1 (0.6)	0	1 (0.3)
Missing	1 (0.6)	1 (0.6)	2 (0.6)
Time from transplant to cGvHD diagnosis (days)			
n	165	164	329
Mean (SD)	371.44 (378.120)	404.53 (749.580)	387.94 (592.439)
Median	247.00	230.00	235.00
Min–Max	20.0–2360.0	35.0–8047.0	20.0–8047.0
Time from cGvHD diagnosis to randomisation (days)			
n	165	164	329
Mean (SD)	232.62 (282.843)	227.24 (287.471)	229.94 (284.737)
Median	174.00	149.50	154.00
Min–Max	7.0–2017.0	10.0–1947.0	7.0–2017.0
SR-cGvHD diagnosis – n (%)			
SR criteria met (any)	165 (100)	164 (100)	329 (100)
A: lack of response or disease progression after prednisone ≥ 1 mg/kg/day for at least 1 week (or equivalent)	62 (37.6)	73 (44.5)	135 (41.0)

Disease history	Ruxolitinib N=165	BAT N=164	All Patients N=329
B: Disease persistence without improvement despite continued treatment with prednisone >0.5 mg/kg/day or 1 mg/kg/every other day for at least 4 weeks (or equivalent)	58 (35.2)	42 (25.6)	100 (30.4)
C: Increase prednisone dose to >0.25 mg/kg/day after two unsuccessful attempts to taper the dose (or equivalent)	45 (27.3)	49 (29.9)	94 (28.6)
Time from initial cGvHD to diagnosis of SR-cGvHD (days)			
n	165	164	329
Mean (SD)	200.84 (259.325)	186.87 (242.706)	193.88 (250.892)
Median	125.00	106.00	111.00
Min–Max	3.0–2009.0	2.0–1540.0	2.0–2009.0
Overall severity of SR-cGvHD at study entry			
Mild	0	1 (0.6)	1 (0.3)
Moderate	68 (41.2)	73 (44.5)	141 (42.9)
Severe	97 (58.8)	90 (54.9)	187 (56.8)
Prior systemic cGvHD / SR-cGvHD therapy – n (%)			
Steroid only	70 (42.4)	81 (49.4)	151 (45.9)
Steroid + CNI	68 (41.2)	69 (42.1)	137 (41.6)
Steroid + CNI + other systemic therapy	10 (6.1)	4 (2.4)	14 (4.3)
Steroid + other systemic therapy	14 (8.5)	9 (5.5)	23 (7.0)
Missing	3 (1.8)	1 (0.6)	4 (1.2)

Abbreviations: aGvHD, acute graft-versus-host-disease; BAT, best available therapy; cGvHD, chronic graft-versus-host-disease; CNI, calcineurin inhibitor; FAS, full analysis set; min, minimum; max, maximum; SD, standard deviation; SR, steroid-refractory.

d) Please also supply the Study CINC424D2301-Primary CSR.

The REACH3 primary analysis CSR has been provided in the new reference pack.

A 5. Section D.1.6 of company submission Appendix D outlines the criteria used to assess risk of bias in the included randomised controlled trials (RCTs). A later section of the same appendix (D.5) shows a tabulation of the output of risk of bias assessment for RCTs. However, a critical appraisal of non-randomised controlled study is lacking (e.g. REACH1).

Please provide assessment of bias in the included non-randomised studies.

Risk of bias assessment for single-arm or non-randomised trials, including REACH1, has now been performed using the Downs and Black checklist (7). A table summarising the results is presented in the document **ID6377-Ruxolitinib-aGvHD_single arm trial quality assessment**. Of the 19 single-arm or non-randomised trials included in the SLR involving aGvHD patients, 18 were suitable for risk of bias assessment; the only exception was Abedin 2022 (NCT03327857), a conference abstract providing insufficient detail for assessment (8). The study with the lowest risk of bias, with 19/27 yes responses on the Downs and Black checklist, was Tan 2017 (ChiCTR-OCH-12002890), a Phase 2 single-arm study investigating basiliximab + etanercept for SR-aGvHD (9). The two oldest studies, Hervé 1990 (10) and Byers 1990 (11), were the studies with the highest risk of bias, with 9/27 and 10/27 yes responses, respectively. The lower scores for these studies reflected a relative lack of detail on methodological considerations such as the pre-specification of analyses, selection of statistical tests, and adjustment for varying lengths of follow-up.

The three Phase 2 single-arm trials involving ruxolitinib – Jagasia 2020 (REACH1 [NCT02953678]) (12), Moiseev 2020 (NCT02997280) (13), and Zhao 2020 (ChiCTR1900024408) (14) – were amongst the studies with the lowest risk of bias, with 16/27, 15/27, and 18/27 yes responses, respectively. As a single-arm, open label trial, REACH1 could not have achieved a score higher than 19/27, given eight questions in the checklist do not apply to single-arm, open label trials. The main limitation of Jagasia 2020 (REACH1 [NCT02953678]) was a lack of reporting on the real-world representativeness of the trial's participants and healthcare facilities. This limitation was shared by 16 of the 18 studies assessed for risk of bias.

Clinical effectiveness evidence

A 6. Priority question: The decision problem states that the population matches that of the NICE scope. However, there are multiple diseases

that can lead to allogeneic stem cell transplant (AlloSCT) and then acute Graft-versus-host-disease (aGvHD).

a) Please provide the baseline characteristics by disease for which AlloSCT was required for the two trials (REACH1 and REACH2).

For patient baseline characteristics by underlying disease (requiring alloSCT), please see Table 3 (Table 10.4, page 120 in the REACH2 final analysis CSR (15)) and Table 4 (Table 1.3.2, page 181 in the REACH1 final analysis CSR (16)).

Table 3: Disease history by treatment – REACH2, FAS

Disease history	Ruxolitinib N=165	BAT N=164	All Patients N=329
Primary diagnosis classification-n (%)			
Malignant-leukaemia/MDS	129 (83.8)	121 (78.1)	250 (80.9)
Malignant-lymphoproliferative	18 (11.7)	26 (16.8)	44 (14.2)
Non-malignant	1 (0.6)	5 (3.2)	6 (1.9)
Other	6 (3.9)	3 (1.9)	9 (2.9)
Diagnosis of underlying malignant disease-n (%)			
Acute lymphoblastic leukaemia	25 (16.2)	16 (10.3)	41 (13.3)
AML	58 (37.7)	63 (40.6)	121 (39.2)
Chronic myelogenous leukaemia	6 (3.9)	2 (1.3)	8 (2.6)
Excess blasts 2, developed from Fanconi syndrome	1 (0.6)	0	1 (0.3)
Hodgkin lymphoma	6 (3.9)	2 (1.3)	8 (2.6)
Multiple myeloma	2 (1.3)	5 (3.2)	7 (2.3)
MDS	26 (16.9)	29 (18.7)	55 (17.8)
Non-Hodgkin lymphoma	9 (5.8)	19 (12.3)	28 (9.1)
Other acute leukaemia	4 (2.6)	3 (1.9)	7 (2.3)
Other leukaemia	6 (3.9)	8 (5.2)	14 (4.5)
Other	4 (2.6)	0	4 (1.3)
Diagnosis of underlying non-malignant disease-n (%)			
Histiocytic disorders	0	1 (0.6)	1 (0.3)
Sickle cell disease	1 (0.6)	1 (0.6)	2 (0.6)
Other	0	3 (1.9)	3 (1.0)
Diagnosis of underlying disease other specify-n (%)			

Disease history	Ruxolitinib N=165	BAT N=164	All Patients N=329
Blastic neoplasm of plasmacytoid dendritic cells	0	1 (0.6)	1 (0.3)
Multiple myeloma and secondary AML	0	1 (0.6)	1 (0.3)
Myelofibrosis	2 (1.3)	0	2 (0.6)
Myeloma	0	1 (0.6)	1 (0.3)
Myeloproliferative neoplasm	1 (0.6)	0	1 (0.3)
Post polycythaemia vera myelofibrosis	1 (0.6)	0	1 (0.3)
Primary myelofibrosis	1 (0.6)	0	1 (0.3)
Septic granulomatosis	1 (0.6)	0	1 (0.3)
Time from diagnosis of underlying disease to screening (year)			
n	154	154	308
Mean (SD)	2.16 (3.195)	1.72 (2.170)	1.94 (2.735)
Median	1.04	0.86	0.94
Min-Max	0.2–25.7	0.2–15.1	0.2–25.7
CIBMTR risk assessment-n (%)			
Low	46 (29.9)	46 (29.7)	92 (29.8)
Intermediate	43 (27.9)	48 (31.0)	91 (29.4)
High	61 (39.6)	55 (35.5)	116 (37.5)
Unknown	4 (2.6)	6 (3.9)	10 (3.2)

Abbreviations: AML, acute myeloid leukaemia; BAT, best available therapy; CIBMTR, Center for International Blood and Marrow Transplant Research; FAS, full analysis set; MDS, myelodysplastic syndrome; min, minimum; max, maximum; SD, standard deviation.

Table 4: Summary of cancer history – REACH1, efficacy evaluable population

	Ruxolitinib N=71
Number (%) of Subjects with Cancer History	71 (100)
Acute myeloid leukaemia	20 (28.2)
Acute lymphoblastic leukaemia	8 (11.3)
Chronic lymphocytic leukaemia	3 (4.2)
Lymphoma	9 (12.7)
Myelodysplastic syndrome	20 (28.2)
Other	11 (15.5)
Time since diagnosis of underlying malignancy (years)	
n	71
Mean (SD)	2.15 (3.288)
Median	1.08

	Ruxolitinib N=71
Min–Max	0.3–26.3
Disease status at time of transplant	
Complete response	50 (70.4)
Partial response	8 (11.3)
Stable disease	5 (7.0)
Relapsed/Refractory	6 (8.5)
Unknown	2 (2.8)

Abbreviations: min, minimum; max, maximum; SD, standard deviation.

b) Please provide the same for patients in UK clinical practice.

Table 3 was validated with UK clinical experts who confirmed that it is representative of UK clinical practice (2). Namely, the experts confirmed that the diagnosis of underlying malignant disease in REACH2 being mainly acute myeloid leukaemia (AML; 37.7%), myelodysplastic disorder (MDS; 16.9%), and acute lymphoblastic leukaemia (ALL; 16.2%) is representative of the UK. Furthermore, this is validated by EBMT activity surveys, with the most recent showing that AML (39.0%), MDS (13.0%) and ALL (17.0%) were the 3 most common indications for alloSCT in 2022, accounting for almost 70% of all indications (17), similar to what was observed in REACH2 (15).

c) Please discuss the implications of any differences between these two in terms of prognosis and treatment effect (ruxolitinib versus best available treatment (BAT).

In line with A6 b), there are no major differences between the patients in the REACH trials and UK clinical practice in terms of the baseline characteristics for which alloSCT was required. This has been validated by clinical expert opinion (2).

A 7. Priority question: The decision problem states that the comparator matches that of the NICE scope. However, there are multiple forms of established clinical management (ECM) that can be used to treat GvHD. Table 20 in the CS appears to show the distribution of different forms of BAT in REACH2, which is different to that based on clinical expert input and as used in the economic analysis.

a) Please provide the complete list of treatments and precise combinations of treatments in the BAT arm of REACH2 with the percentage of patients who receive them.

As part of the REACH2 exclusion criteria patients were not permitted to receive more than one systemic treatment for SR-aGvHD, therefore there were no treatment combinations. However, some concomitant medications were permitted, including systemic therapies, and patients could continue systemic corticosteroids, CNIs and other systemic treatments if used for aGvHD prophylaxis only. For the complete list of concomitant treatments in both the ruxolitinib and BAT arms within REACH2 please see pages 127–128 of the REACH2 final analysis CSR. Please see Table 8, page 43 of the CS, the relevant section of which is shown here in Table 5, for the list of supportive treatments that patients were allowed to receive for the management of SR-aGvHD.

Table 5: Summary of trial methodology -REACH2, concomitant medications

	REACH2
Permitted and disallowed concomitant medication	**The following medications were permitted:** Supportive treatments for management of patients with SR-aGvHD**,** systemic corticosteroids, CNI, topical corticosteroid therapy, aGvHD prophylaxis medications, antibiotics, anti-infectives, immunisations, additional supportive care measures. **The following medications were disallowed:** Aspirin, NSAIDs or related medications, concomitant use of another JAK inhibitor, investigational medication, chemotherapeutic agents and/or non-schedules DLI, pre-emergent intervention related to graft failure or haematological disease relapse/progression, Fluconazole at daily doses higher than 200 mg.

Abbreviations: CNI, calcineurin inhibitor; DLI, donor lymphocyte infusion; JAK, Janus kinase; NSAID, non-steroidal anti-inflammatory; SR-aGvHD, steroid-refractory acute graft-versus-host-disease

b) Please provide a list of treatments that are ECM in the UK with the percentage of patients who receive them.

Please see Table 20 in the CS for the full list of ECM treatments and their respective proportions, which were validated by UK clinicians during the advisory board we conducted (18). Additionally, please see in Table 20, page 136 of the CS the scenario “BAT per clinician survey", whereby we have included the results of a recent survey conducted independently by a clinician, which was sent to all

transplant centres in the UK. In that survey, the use of a couple of treatments, that are not in REACH2, were reported, namely basiliximab (1.7%) and alemtuzumab (0.2%). These treatments were used in one single centre each and therefore are not representative of overall usage in the UK. If the EAG would like more details with regards to this survey, the clinical expert who conducted the study can be contacted directly to provide further details. Please note that this survey was the clinical expert's own study, and we can only share aggregate data, to comply with GDPR.

c) **Please discuss the implications of any differences between UK ECM and BAT in REACH2 in terms of prognosis and treatment effect (ruxolitinib versus BAT).**

In line with question A7 d) i), Figure 14 of the CS showing FFS by the different BAT was presented to UK clinical experts who agreed that the efficacy is comparable among all the treatments and is consistent with clinical experience. Therefore, the clinical experts confirmed there were no major differences between UK established clinical management (ECM) and BAT in REACH2 in terms of prognosis and treatment effect, and adjusting the proportions of patients who receive each BAT to reflect a difference in costs was appropriate.

d) **Please present evidence as to the relative effectiveness of each of the forms of ECM/BAT and consider adjusting the treatment effect from REACH2 to reflect any difference in distribution between the trial and the economic model/UK clinical practice.**

    i. **In accordance with question A2, please perform an analysis comparing ruxolitinib with ECP.**

As noted on page 99 of the CS, the comparator used in this submission is BAT (also referred to as ECM without ruxolitinib), which is in line with the NICE final scope, DP and the pivotal REACH2 trial. This comparator has also been validated by UK clinical experts, who agreed that an analysis looking at the relative effectiveness as shown in Figure 14 of the CS is not warranted, as the efficacy is similar. Additionally, this analysis breaks randomisation and is inconsistent with the approach taken in TA949

(19), which used ECM/BAT as the comparator. Based on these reasons, this analysis has not been provided in response to this question.

ii. **In accordance with question A2, please perform an analysis comparing ruxolitinib with a comparator formed by all types of BAT except ECP**

As discussed in A7 d) i), the comparator used in this submission is BAT which is in line with the NICE final scope DP, the pivotal REACH2 trial as well as other trials in GvHD. Given that this comparator has also been validated by UK clinical experts (and that efficacy among BAT treatments is considered to be similar), we do not consider it is warranted to provide an analysis which excludes ECP from BAT. Additionally, the analyses requested by the EAG as part of this question and A7 d) i) are inconsistent with the recent belumosudil appraisal TA949 i.e. BAT was considered to be the appropriate comparator. In Table 12 on page 40 of the NICE committee papers in TA949, some uncertainty was identified surrounding the proportion of patients receiving each treatment (as these were not reflective of UK clinical practice), which prompted an analysis whereby the % of patients on each BAT was adjusted in line with clinical expert opinion to reflect UK clinical practice. However, a re-analysis comparing belumosudil to a single BAT treatment or narrow selection of treatments was not deemed reasonable, particularly as this would break randomisation and would be subject to bias.

e) **According to Table 20, 3% received no treatment. Please explain this and re-estimate all clinical effectiveness outcomes excluding these patients.**

We consider the ITT analysis to be the most appropriate data for estimation of clinical effectiveness outcomes. The request to exclude 3% of patients who did not receive treatment (in the BAT arm) may not be appropriate (breaking randomisation) and could introduce additional uncertainty. Additionally, some patients in the ruxolitinib arm also did not receive treatment (1.3%). The base-case approach we have taken appropriately uses the ITT data and therefore minimises uncertainty within the analysis. Additionally, UK clinical experts agreed that this analysis is warranted in this context (2). It is common for a minority of patients not to receive

treatment in clinical trials, and this could be for various reasons, including the patient's current disease state or quality of life, and therefore no treatment may be considered by the clinician to be the most appropriate management strategy at the time. Using the ITT data adequately capture the reality of the clinical trial.

Despite these limitations, for transparency, the analysis of FFS (with cGvHD included as an event, as per the model) and OS have been presented for the patients in each arm who received treatment compared with the ITT analysis (Figure 1 and Figure 2). In both cases, the curves for ruxolitinib are identical, as both patients are censored before any events occur. For the BAT arm, the curve for treated patients sits slightly below the ITT curve, but the difference is negligible.

Figure 1: FFS for the ITT population and patients who received treatment

Abbreviations: BAT, best available therapy; FFS, failure-free survival.

Figure 2: OS for patients who received treatment

Abbreviations: BAT, best available therapy; OS, overall survival.

f) Please clarify the criteria applied for investigator choice of BAT.

i. Do they correspond to those described in question A2 i.e. haematological stability and venous access?

As outlined on p.86 of the REACH2 CSR, patients received BAT based on the investigator's best judgment, taking into account several factors including the manufacturer's instructions, labelling, patient's medical condition, institutional guidelines for any dose adjustment, risk of infection, prior clinical experience, as well as access to the chosen BAT. Status of haematological stability and venous access was not explicitly required for separate consideration, although these factors may have been considered through assessment of 'patient's medical condition' and / or institutional guidelines.

Was there no lack of access to ECP?

In line with question A7 f) i), investigator's judgement included several factors, including access to the chosen BAT. Therefore, there is a possibility that some patients experienced a lack of access to ECP.

A 8. Priority question: In the REACH trials there are multiple types of previous and concomitant treatments and treatment combinations.

a) Please provide a list of first line treatments and treatment combinations in the UK with the percentage of patients who receive them.

Based on clinical expert opinion first-line treatment for SR-aGvHD in the UK includes either steroids and CNIs, or steroids, CNI, and another aGvHD prophylaxis and/or treatment. Table 10-5, p124 of the REACH2 CSR and Table 2, Section M.1.2.1 of Appendix M was shown to clinical experts who validated that the list of first line treatments received by patients in REACH2 is representative of UK clinical practice. Due to time constraints, validation of the REACH1 corresponding tables were not conducted, as the data were used as supportive evidence only in the CS.

b) Please discuss the implications of any differences between these first line treatments and combinations and those found in the REACH trials in terms of prognosis and treatment effect (ruxolitinib versus BAT).

Based on clinical expert opinion, there are no major differences between the first line treatments and combinations used in UK clinical practice and those in the REACH trials.

c) Please provide a list of treatments and treatment combinations used in combination with ECM and likely to be used in combination with ruxolitinib in the UK with the percentage of patients who receive them.

Based on clinical expert opinion, treatments likely to be used in combination with ECM and likely to be used in combination with ruxolitinib in the UK are mainly steroids and CNI. It may be that MMF is also used in addition to steroids and CNI in a minority of patients

d) Please discuss the implications of any differences between these concomitant treatments and combinations and those found in the

REACH trials in terms of prognosis and treatment effect (ruxolitinib versus BAT).

The clinical expert noted that MMF is an adjunctive therapy which is not considered toxic and is easy to add in clinical practice, and it is something which is unlikely to make a difference to prognosis or treatment effect. Therefore, the clinical expert explained that the fact MMF was given as a separate BAT as opposed to in combination will not have an effect on prognosis or treatment effect.

A 9. Priority question. The CS mentions the possibility of tapering of treatment: "…*first for corticosteroids, followed by CNI and ruxolitinib*." (p. 41) Please clarify how the rules for tapering off in the REACH trials would compare to those in clinical practice and discuss any implications for prognosis and treatment effect (ruxolitinib versus BAT).

UK clinical experts confirmed that the tapering of treatment within the REACH trials is reflective of UK clinical practice. The expert explained that corticosteroids are the first treatment to taper due to the adverse effects of long-term exposure, followed by CNI, and lastly by ruxolitinib. Tapering guidelines from the REACH2 trial were shown to clinical experts who agreed they were appropriate and reflective of UK clinical practice:

Tapering of immunosuppression will follow 2 steps: first taper of corticosteroids, and followed with taper of CNI/ruxolitinib in responding patients.

During the Treatment Period in both the ruxolitinib and BAT arms, immunosuppression taper guidelines are:

- *Corticosteroids: 10% dose reduction every 5 days in patients demonstrating CR/PR as observed by the Investigator, beginning no earlier than Day 7 and continuing to approximately Day 56 to allow 7-8 week taper.*
- *CNI (cyclosporine or tacrolimus): 25% dose reduction per month starting from Day 56 in patients demonstrating complete resolution of all signs/symptoms of aGvHD, once off systemic corticosteroids.*

- *Ruxolitinib: 50% dose reduction every 2 months (56 days) initiated at Day 56 in responding patients, once off systemic corticosteroids. Initial dose reduction is to 5 mg orally BID. If sustained aGvHD stable disease is observed, patient is further tapered by a second 50% dosage reduction to 5 mg orally QD for an additional 56 days, prior to cessation.*

There are no major differences between the tapering of treatment in the REACH trials and UK clinical practice therefore there are no implications for prognosis and treatment effect. For further information surrounding tapering guidelines adhered to within the clinical trials, please see the REACH2 and REACH3 protocols (20, 21) and REACH1 final CSR (16).

A 10. Priority question. In Table 7 of the CS, failure free survival (FFS) is defined as including *"signs or symptoms of cGvHD"* in REACH1, but in REACH2 it is stated that *"the competing risk was cGvHD".*

a) Please provide the list of events that would count as 'failure' in FFS for both REACH1 and REACH2.

The following events counted as failures in FFS in both REACH1 and REACH2:

- Additional therapy/new systemic treatment for aGvHD
- Relapse/progression of underlying disease

In both trials, mortality was counted as failure, but in REACH2, this was specified to be non-relapse mortality, whereas in REACH1, death of a patient, regardless of cause, counted as failure.

b) Please explain why the REACH1 definition was different to the REACH2 definition.

As the two clinical trials were run by two different sponsors (Incyte for REACH1 and Novartis for REACH2), the method to analyse the FFS was different. Both methods are relevant, and we do not expect a significant difference especially when the number of patients who reported competing risks is limited.

c) **Please explain what is meant by 'competing risk': is this a censoring event?**

A competing risk is an event that can occur that would preclude the event of interest. These are not considered as censoring events in the CSR analyses, rather the cumulative incidence function is estimated, accounting to competing events. In the analysis for the economic model, any competing events are treated as censoring events. See the response to D1 for additional details.

d) **Please explain why cGvHD is specifically mentioned as a competing risk.**

In the analysis of FFS, this incidence of cGvHD is considered a competing risk as it leads to a series of potential events that are unrelated to the treatment of aGvHD. For example, incident cGvHD is likely to require additional systemic treatment unrelated to aGvHD, and introduces additional sources of mortality. As such, patients may fail, however this is not related to aGvHD.

Adverse events

A 11. Priority question. Please present a summary of adverse events (AEs) for the randomised treatment period separately by each type of BAT (including ECP separately). This summary should include the following: serious AEs any fatal AE, and any grade 3+ AE, and any AE leading to discontinuation, presented as in Table 17 of the CS with both follow-up time points.

As stated in question A7 d) i), the comparator in the final scope and DP is ECM without ruxolitinib, which is equivalent to BAT (a basket of therapies). This was further validated with UK clinical experts. The CS therefore looks at BAT, and we consider that it is not warranted to separate and analyse each of the individual treatments as suggested in this question. Please see Section B.2.10.1 in the CS for a summary and further detail relating to BAT adverse events.

Section B: Clarification on cost-effectiveness data

Model structure

B 1. Priority question. Please answer the following questions regarding the modelling of chronic GvHD (cGvHD).

a) Please provide a clear definition of the cGvHD population that is included in the economic model and discuss if this can be considered the same as in REACH3 (in REACH3 for example, one of the exclusion criteria is "Patients that transition from active aGvHD to cGvHD without tapering off corticosteroids ± CNI and any systemic treatment").

The cGvHD population that is included in the economic model is patients who first had aGvHD and developed cGvHD before or after the symptoms of aGvHD were resolved.

The economic model uses data from REACH3 to model outcomes for patients developing chronic GvHD. The population in REACH3 includes patients with aGvHD prior to cGvHD and patients with *de novo* cGvHD. In REACH3, 88 of 164 patients (53.7%) in the BAT arm had prior aGvHD and 17 (10.4%) of these had SR-aGvHD. While we acknowledge some potential differences in population between those with *de novo* cGvHD and those in the economic model, clinical experts considered it was reasonable to use the overall data from REACH3 as a proxy and that outcomes in REACH3 are broadly reflective of those they would expect in those developing chronic GvHD in the model (18, 22).

Figure 3 presents FFS in the BAT arm of REACH3 by aGvHD status respectively, with no apparent difference in outcomes between the groups, indicating that outcomes from REACH3 as a whole are generalisable to patients with prior aGvHD.

Figure 3: FFS in REACH3 by prior aGvHD status

Abbreviations: aGvHD, acute graft-versus-host-disease; FFS, failure-free survival.

Within REACH3, the overall population was selected, as there were no clear differences between the prior aGvHD and no prior aGvHD populations. Using the data from REACH3 allows for a more granular approach to modelling cGvHD, with failure of treatment and relapse accounted for, and provides a more accurate reflection of the patient pathway.

b) **On page 41 of the CS, it is mentioned that (from end of treatment (EOT) to Month 24): all patients were followed up for long-term observation up to 24 months from randomisation. During this period, long-term data was collected on any occurrence of cGvHD (among many other outcomes). Please clarify if occurrence of cGvHD can only happen after EOT or not and how this has been included in the cost effectiveness model.**

In REACH-2, the occurrence of cGvHD was captured from trial entry, and therefore the transition to cGvHD was captured during both the treatment period (up to month 24) and beyond. This is reflected in the economic model where patients can move to the cGvHD health from model entry.

The incidence of cGvHD, or requirement for NST did not require patients in REACH2 to stop treatment. As such, the model does not assume that treatment will stop once patients exit the FF state and models the observed treatment duration for each patient.

c) **Please explain what the underlying reason is for having more patients developing cGvHD in the ruxolitinib arm, and if it is something to be observed in real practice. How is that related to the median onset time of cGvHD being [redacted] in the ruxolitinib arm?**

Overall survival is higher in the ruxolitinib arm than the BAT arm, and the longer aGvHD patients survive, the higher the chance of them developing cGvHD. In the model, patients in the BAT arm spend 0.64 years in the FF and NST states, where they are at risk of cGvHD, compared to 1.09 years in the ruxolitinib arm. As a result, there are more patients remaining at risk of cGvHD at later time points, and so ruxolitinib has a longer median onset time. This is consistent with what is observed in REACH2.

Additionally, separate models have been fit for the incidence of cGvHD in the ruxolitinib and BAT arms, which led to higher rates of cGvHD at later time points for ruxolitinib. Clinical validation was sought following receipt of the clarification questions and indicated that they did not expect the incidence of cGVHD to be different between BAT and ruxolitinib (after accounting for the competing events) and it is more appropriate to assume the same incidence in both arms. Consequently, the model base case has been updated to the same rate of cGvHD for both arms, estimated form the pooled ruxolitinib and BAT data from REACH2.

Figure 4 presents the incidence of cGvHD over time in each arm. The total incidence of cGvHD remains higher in the ruxolitinib arm, with a longer median time to cGvHD (0.69 years vs 0.54 years in the BAT arm). As stated in our response above, this is because patients in the ruxolitinib arm stay at risk of cGvHD for longer, as they survive longer.

Figure 4: Incidence of cGvHD assuming the same rate of cGvHD in each arm

Abbreviations: BAT, best available therapy; cGvHD, chronic graft-versus-host-disease.

The updated base case (also corrected in line with the responses to questions B18, B19 and C5) results in an ICER of £25,161. Full updated results are presented in the appendix.

d) **It seems from the time-to-event curves in the model that patients will have better outcomes once they develop cGvHD. Please discuss the validity of this, if indeed it happens in the model, because it seems counterintuitive. In order to do so, please provide any evidence such as expert opinion, relevant publications, and/or plots comparing survival/hazard curves for i) BAT patients in aGvHD vs. BAT patients in cGvHD and ii) ruxolitinib patients in aGvHD vs. ruxolitinib patients in cGvHD.**

According to UK clinical experts, it is important to consider it is not the case that aGvHD patients who develop cGvHD do "better", rather to consider that the alternative to developing cGvHD is death or relapse of their underlying malignancy.

Figure 5 presents OS (from randomisation) in REACH2 for patients who do and do not go on to develop cGvHD, and shows much higher survival amongst those with cGvHD.

Figure 5: Overall survival by cGvHD status

Abbreviations: cGvHD, chronic graft-versus-host-disease.

e) **On page 81 of the CS, it is mentioned that patients will stay in the FFS state 'until they experience treatment failure as defined in the REACH2 trial (receive a new systemic aGvHD therapy, experience a relapse of their underlying malignancy, or experience non-relapse mortality)'. Also, on page 83 a similar description is provided of what consists of a 'failure' event for FFS. Please explain why and how the transition to cGvHD from FFS has been then modelled when the definition of FFS does not include cGvHD. Does it occur that the estimation of FFS includes both patients with acute and chronic GvHD? Please explain what is meant with the statement 'within the assessment of FFS, the development of cGvHD was treated as a competing risk' on page 83.**

In the assessment of FFS used in REACH2, patients are followed up until they have a failure event, are lost to follow-up, or develop cGvHD. Each patient in the data set has a failure time and an event marker, which indicates what occurred at that time, which can take the following values:

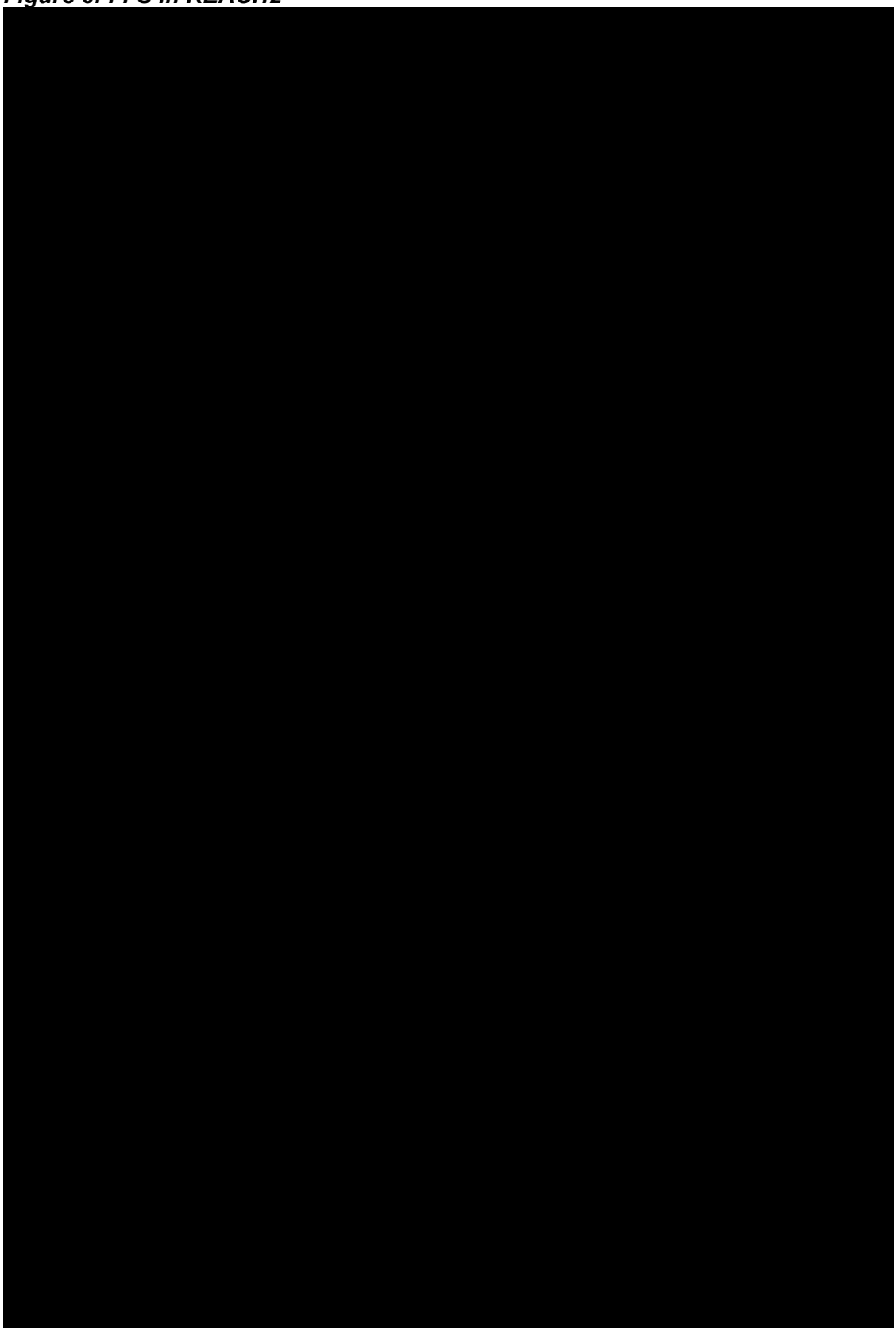
- Lost to follow-up

- Receive a new systemic treatment
- Relapse of underlying malignancy
- Non-relapse mortality
- Incident cGvHD.

This is the approach used to generate Figure 11-5 in the REACH2 final analysis CSR, and shown in Figure 6. This shows FFS by treatment, giving the cumulative probability of each event over time, and is the same as the cumulative incidence function described in Putter et al, with cGvHD as a competing event.

These are the data used to generate the transitions from the FF state in the model, as it provides the time from randomisation to the first of the 4 events of interest. Thus, while the FFS data from REACH2 has been used to generate these probabilities, the probability of remaining in the FF state is not equivalent to the probability of being failure-free according to the FFS analysis, and it may be more accurate to refer to this state as 'Failure-free, without cGvHD'.

Figure 6: FFS in REACH2



Abbreviations: aGvHD, acute graft-versus-host-disease; BID, twice daily; cGvHD, chronic graft-versus-host-disease; FFS, failure-free survival.

Results from the analysis of FFS that does not take cGvHD into account (i.e. patients continue to be followed-up after incidence of cGvHD) are also presented in the REACH2 final analysis CSR, Figure 11-6, however this analysis is not used in the economic model.

f) **Please clarify how the assessment of FFS was adjusted for competing risks.**

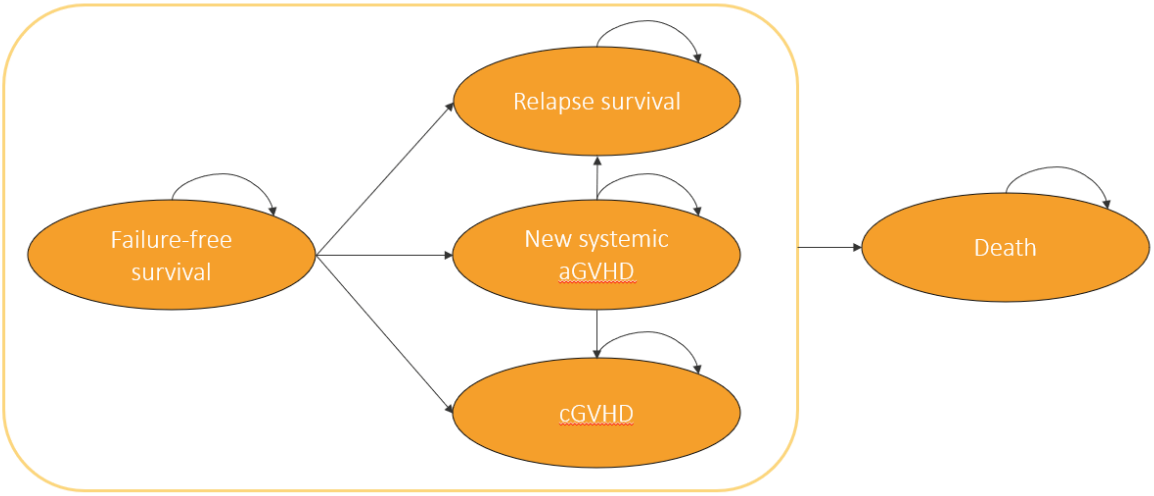
In the analysis of REACH2, as stated in response to d), FFS was assessed using the cumulative incidence function as described by Putter et al.

In the economic model, and in line with TSD19, in the analysis of transition probabilities where more than one event is possible, competing risks have been allowed for by defining the time to the event of interest, with other competing risks treated as censoring events. The time-to-event curve used to generate the transitions from the failure free state would more accurately be described as the time to failure or incident cGvHD.

g) **Please clarify if patients can transition from relapse (after aGvHD failure free) to cGvHD. There seems to be a contradiction in the CS as on page 81 it is stated that 'patients can enter the cGvHD failure-free state from any of the aGvHD health states' whilst on page 83 it is stated that 'patients are assumed not to transition from relapse to cGvHD'. If necessary, please also amend Figure 13. In addition, please clarify if patients in relapse receive any treatment for their underlying malignancy and if this aligns with clinical practice in the UK.**

Patients cannot transition from aGvHD relapse to cGvHD because in the majority of cases, a relapse of the underlying malignancy leads to a resolution of GvHD. In addition, there are no patients transitioning from aGvHD relapse to cGvHD in REACH2. Figure 13 has been updated to Figure 7.

Figure 7: Model structure – Figure 13 of the CS



Abbreviations: aGvHD, acute graft-versus-host disease; cGvHD, chronic graft-versus-host disease; CS, company submission.

B 2. Priority question. Regarding the definition of the health states in the model (FFS, NST, Relapse, etc.):

a) Please discuss the differences in the prognosis of patients in the NST health state and those with incident cGvHD. Please comment on the face validity of having these two health states in the model. Please also explain what the differences in treatments between these two patient groups in clinical practice would be.

Patients in the NST state are aGvHD patients without cGvHD who have required additional systemic treatment and, in line with clinical opinion, will have different morbidity and mortality to those with incident cGvHD. Patients in the cGvHD state in the model may or may not have resolved aGvHD, and REACH3 enrolled patients with both interrupted and progressive disease. QoL differs between acute and chronic disease, as different organs are affected. The clinical experts stated that the determinants of QoL are very different between acute and chronic patients. For acute patients, the primary concern is survival as they are in a life-threatening situation. For example, some patients may suffer with 4 litres of diarrhoea per day and are completely bed-bound – their QoL is extremely poor. For chronic GvHD patients, QoL is primarily about mobility, functionality, and the ability to perform daily tasks such as dressing, maintaining sexual function, and ability to work (22).

While ECP is the most common treatment for both acute and chronic disease, there are differences in the treatment patterns between the diseases. Patients with cGvHD may be treated with rituximab or imatinib, while anti-thymocyte globulin (ATG) and MSCs are not options for cGvHD. The duration of treatment for patients with cGvHD is also typically far longer than for those with aGvHD. Additionally, patients with cGvHD are eligible for treatment with belumosudil, which is not licensed for aGvHD.

b) **Patients in the NST health state (of aGvHD) can enter the cGvHD health states only via the cGvHD failure-free health state. Please comment on the rationale and clinical plausibility of this assumption.**

In line with the REACH trials, while NST within aGvHD is a result of treatment failure, cGvHD is not a failure event of aGvHD. It is a competing risk of aGvHD. Therefore, patients start from cGvHD failure-free when cGvHD is initially developed. cGvHD patients who experience treatment failure and require NST will transition to the cGvHD NST health state.

In line with clinical opinion, a patient who fails treatment for aGvHD then develops cGvHD is not equivalent to a patient who develops cGvHD from the FF state, then fails treatment for cGvHD, as these are separate diseases, with different prognoses and treatment patterns. Specifically, a patient who moves to the NST state then develops cGvHD would not initially be eligible for treatment with belumosudil.

c) **Please clarify if patients in the cGvHD failure-free health state (incident cGvHD patients) are expected to receive 1L treatment as defined for cGvHD patients. Please explain why cGvHD NST patients are assumed to receive 3L treatment instead of 2L treatment for cGvHD.**

As the population in the decision problem is patients with aGvHD aged 12 years and older who have an inadequate response to corticosteroids, and steroids are typically the 1L treatment for both aGvHD and cGvHD (23), patients who transition from aGvHD to cGvHD have already received 1L treatment for cGvHD. Although it is possible for those patients to be treated with steroids again after transitioning to cGvHD from aGvHD for up to 5 days, these patients usually will not respond to steroids in such a short time and will be put on the next line of treatment within 5

days, based on UK clinical experts' opinion (22). More commonly, patients will receive a treatment other than steroids for failure-free cGvHD patients who transitioned from aGvHD. Therefore, treatment used in the failure-free cGvHD health state is viewed as a 2L treatment. As for patients with cGvHD who experience a failure and require a new systemic therapy, they will receive 3L treatment.

B 3. Priority question. Please answer the following questions regarding the modelling of treatment effect waning.

a) Please explain why the approach to model treatment effect waning has not been described in the company submission. Please provide a detailed description of the waning approach used in the scenario analysis (and implemented in the model) and explain the rationale behind this.

The approach to treatment waning is described in Table 50 of the company submission. At a specified time point in the model, transition probabilities for patients in the ruxolitinib arm are set equal to the transition probabilities for BAT. In the company scenario analysis, 3 years was selected as this represents the end of follow-up in REACH2. By the end of trial, most patients have experienced treatment failure or incident cGvHD and at Year 3 in the model, the probability of transitioning to NST, relapse or death has approached 0 in both arms, with only minimal differences in transition probabilities. As such, the impact of treatment waning is minimal and driven by differences in the incidence of cGvHD (see part c).

According to UK clinical experts, immune-tolerance usually develops around 2 years when patients are on ruxolitinib, and no patients stay on ruxolitinib for more than 2 years in clinical practice, therefore the REACH2 trial is long enough to capture the impact of treatment waning of ruxolitinib. In addition, by the end of second year in REACH2, most patients have experienced treatment failure or incident cGvHD and at Year 3 in the model, the probability of transitioning to NST, relapse or death has approached 0 in both arms, with only minimal differences in transition probabilities. As such, the impact of treatment waning is minimal and driven by differences in the

incidence of cGvHD (see part c). Therefore, a simple approach was deemed sufficient.

A scenario where treatment waning after 2 years is also considered, with the results discussed in response to part c).

b) Please explain if, given the evidence on duration of response and time on treatment, a lifetime treatment effect (no waning) is justified.

The company submission does not assume a lifetime treatment effect, with the base case including treatment waning from end of the trial follow up period.

As illustrated in B3 a), most patients have experienced treatment failure by the end of second year in both the ruxolitinib and BAT arms in REACH2. The impact of treatment waning is minimal after two years. Treatment waning effect has been implicitly captured in the clinical data during the trial period. As such, treatment waning effect after clinical trial and its impact on model results is minimal.

c) The model results when treatment effect waning is assumed seem to be incorrect or at least counterintuitive, as the ICER improves when waning is assumed. Usually the opposite occurs, which intuitively makes more sense. Please explain why this happens and, if it is the result of an error in the model, please correct it.

This is driven by a reduction in the rate of cGvHD in the ruxolitinib arm, rather than a mistake in the economic model

As explained in B.10.3.4 in the CS, the development of cGVHD has a negative impact on the ICER due to the low quality of life and high cost in this health state. In the scenario without waning, lower rates of cGVHD are observed in the ruxolitinib arm. This is because in the original base-case a higher incidence of cGVHD was assumed for ruxolitinib, and therefore without waning patients on ruxolitinib were more likely to develop cGVHD. When waning is included, the same rate is assumed after 3 years, and therefore patients on ruxolitinib are less likely to develop cGVHD. However, as acknowledged in QB1 of CQ, clinical experts considered that it was not

appropriate to use different incidence of cGVHD for ruxolitinib and BAT and therefore the company base-case has been amended to reflect this.

In the updated base case analysis without treatment waning, the ICER for ruxolitinib is £25,161, increasing to £25,165 with waning applied. The impact of waning is minimal, as by Year 3 there is very little difference in transition probabilities between arms. With waning applied at Year 2, the ICER increases to £25,164. This is higher than without waning, as patients spend less time in the FF state. However it is lower than when it is applied at Year 3, as fewer patient transition to cGvHD.

B 4. Priority question. Please provide a detailed description of the treatment pathway in NHS practice of patients with cGvHD that come via the aGvHD. How would that treatment pathway be different from that of patients that experience directly cGvHD after alloSCT. Please clarify if the treatment pathway of patients in REACH3 would appropriately reflect the NHS practice for patients developing cGvHD after aGvHD. Please provide relevant details from the REACH3 trial and NHS practice to support your answer.

According to NHS treatment guidelines for GvHD (23) patients who experience cGvHD directly after alloSCT receive corticosteroids as 1L treatment for cGvHD. Sirolimus is a 2L treatment for cGvHD, with pentostatin, ECP, rituximab and imatinib also being recommended.

According to UK clinical experts, patients who move from aGvHD to cGvHD and patients who experience cGvHD only have a similar treatment sequence; they will receive steroids, CNI, and in some cases MMF as first line. The only difference is, at the point at which they develop cGvHD, they are at a higher line of therapy. UK clinical experts consulted at the advisory board confirmed that REACH3 distribution of BAT reflected UK clinical practice with the exception of ibrutinib and infliximab which are not used in the UK in second line treatment of cGvHD. UK clinical experts stated that ECP is used in 35% of patients at third line cGvHD, and belumosudil is used in a further 35% of patients, with the remaining patients receiving MMF, imatinib, sirolimus, and rituximab in equal proportions. In addition, UK clinical experts

suggested that although belumosudil is currently used in 35% of patients, this is likely to increase in the future. Therefore, these adjusted proportions have been included in the economic model.

Intervention and comparator

B 5. Priority question. Table 2 in the CS indicates that "Ruxolitinib is indicated for the treatment of patients aged 12 years and older with chronic graft versus host disease who have inadequate response to corticosteroids". Please clarify why ruxolitinib has not been included in the model as a treatment option for patients with cGvHD.

Although ruxolitinib is licensed for patients with cGvHD aged 12 and above who have an inadequate response to corticosteroids, it is not recommended by NICE, based on a terminated appraisal (24). It is, therefore, not part of the treatment pathway for cGvHD patients in England and Wales. UK clinical experts stated that, currently, ruxolitinib is available for a minority of patients who self-fund or have private insurance only (22).

B 6. Priority question. In the CS, it is explained that BAT in REACH2 is not representative of UK practice. In the model, it is assumed the proportions of the different components of BAT only affects costs. Please explain in detail how equal effectiveness of all BAT components can be derived from Figure 14 and 15 in the CS. If necessary, please provide additional evidence to support the assumption of equal effectiveness of BAT components. In addition, please provide figures similar to Figure 14 and 15 but for OS in REACH2 instead of FFS.

As outlined in response to question A7), Figure 14 of the CS showing FFS by the different BAT treatments was presented to UK clinical experts who agreed that the efficacy is comparable amongst all the treatments, and that this is representative of UK clinical practice. Therefore, the clinical experts confirmed there were no major differences between UK ECM and BAT in REACH2 in terms of prognosis and treatment effect, and adjusting the proportions of patients who receive each BAT to reflect a difference in costs was appropriate.

Figure 14 of the CS shows consistency in FFS across the different BAT treatment, with 25% of patients failing within 1 month on all treatments, median survival between 0 and 2 months for all treatments and 75% failing between 1.2 and 4.3 months. The only exception to this is everolimus, however this represents 2 patients. Additionally, the graph shows the results of a log-rank test, which tests for differences in the survival functions, found no significant differences.

Figure 15 of the CS compares ECP with all other BAT options, as ECP is the most commonly used treatment in UK clinical practice. The KM curves for ECP and other BAT are well aligned. The hazard ratio reported from a Cox model is insignificant and close to 1, suggesting no difference in FFS.

As requested by the EAG, these graphs are repeated for OS in Figure 8 and Figure 9. Despite some visual differences, differences were not statistically significant and clinical experts did not expect any difference between ECP and other treatment. Therefore, clinical experts considered it was appropriate to adjust the cost for BAT to reflect the distribution expected in UK practice, and that efficacy for BAT as a whole would not change significantly. For transparency, a scenario analysis was presented in the CS (Table 51) using the BAT distribution from the REACH-2 trial to align cost and efficacy, and results did not change materially.

Figure 8: OS by BAT in REACH2

Abbreviations: ATG, anti-thymocyte globulin; BAT, best available therapy; ECP, extracorporeal photopheresis; MMF, mycophenolate mofetil; MSC, mesenchymal stromal cells; MTX, methotrexate; OS, overall survival.

Figure 9: OS for ECP and other BAT treatment options

Abbreviations: BAT, best available therapy; ECP, extracorporeal photopheresis; HR, hazard ratio; OS, overall survival.

Transition probabilities

B 7. Priority question. Please clarify the difference between Figures 8 and 16 in the CS.

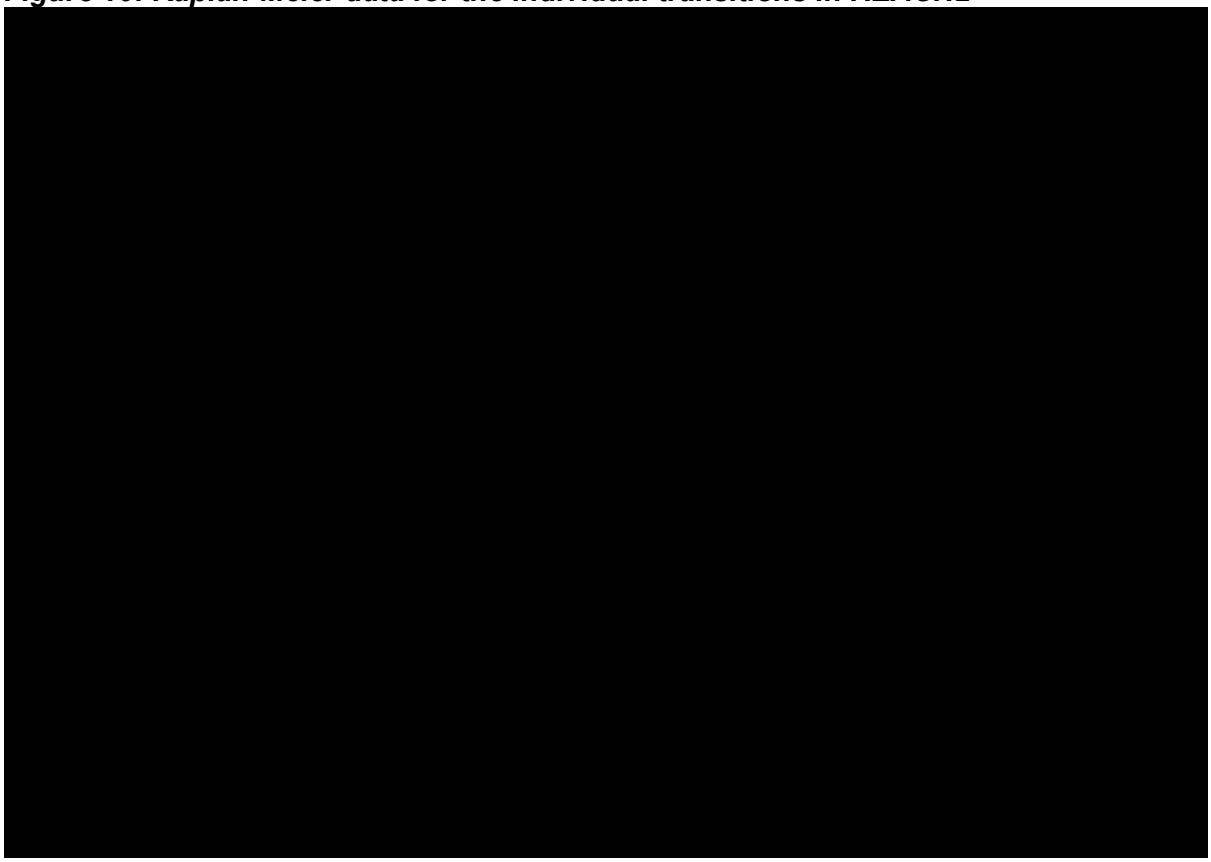
The difference between Figures 8 and 16 in the CS is due to different censoring criteria and included events. Figure 8 of the company submission is taken from the REACH2 CSR final analysis of FFS, which does not include cGvHD as a censoring event. Figure 16 of the company submission is survival in the failure-free state in the model and includes incident cGvHD as an event.

B 8. Priority question. Regarding Figure 17 of the CS:

a) Please include the number of patients at risk for each of the four panels of this figure.

Figure 17 of the CS is updated in Figure 10 below with the number of patients at risk for each of the four panels included. Combined results of ruxolitinib and BAT are included to align the result presenting in Figure 21 of the CS.

Figure 10: Kaplan-Meier data for the individual transitions in REACH2



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

b) Please explain in what terms the curve representing the 'Time to death' (top right curve of Figure 17) is different than Figure 6 (unadjusted for cross over) and Figure 7 (adjusted for cross over) of the CS that represent OS data from REACH2. Please explain why OS survival is higher in the 'Time to death' curve of Figure 17 compared to Figure 7.

Figure 6 (unadjusted for crossover) and Figure 7 (adjusted for crossover) in the CS are overall OS KM data from REACH2 while Figure 17 in the CS is KM data of aGvHD failure-free survival to death only, censoring on other events.

c) If the 'Time to death' from Figure 17 is correct, and has been used to inform OS in the model of patients in aGvHD please explain the

plausibility of these OS especially because as stated on page 11 of the CS "patients with steroid-refractory acute GvHD (SR-aGvHD) have poor survival, with only 25% of patients alive 2 years after diagnosis, decreasing further to 10% at 4 years."

As mentioned in B8 b), Figure 17 in the CS does not relate to the OS KM data of aGvHD. It shows instead the KM data of aGvHD failure-free survival to death only.

B 9. Priority question. Please include the number of patients at risk in each of the panels in Figure 21 of the CS.

Figure 21 of the CS is updated in Figure 11.

Figure 11: REACH2 – KM data for transitions for ruxolitinib and BAT

Abbreviations: BAT, best available therapy; cGvHD, chronic graft-versus-host-disease; KM, Kaplan-Meier; NST, new systemic therapy.

B 10. Priority question. Section B.3.3.2.2.3 of the CS presents the data used to inform the transition probabilities within the cGvHD health states. Figure 22 presents the FFS KM curve for BAT based on REACH3 data but has not presented separate curves for the transitions from cGvHD

failure-free to death, to cGvHD Relapse or to cGvHD NST. Please confirm if separate curves have been used to inform these transitions and provide the missing survival curves including the number of patients at risk. Accordingly, please also provide the curves that were used to inform the transitions from cGvHD NST to Relapse and to death and from cGvHD Relapse to death (with number of patients at risks included). In addition, we have noticed that in the model all relevant survival curves seem to be present. However, for those describing transitions from the cGvHD health state, the KM curves are missing. Please add them to these plots.

Curves for the transitions from cGvHD failure-free to cGvHD NST, to death or to cGvHD relapse are presented in Figure 12. Curves for the transitions from cGvHD NST to cGvHD relapse or to death, or cGvHD relapse to death are presented in Figure 13.

Figure 12: Kaplan-Meier data for the individual transitions in REACH3

Abbreviations: BAT, best available therapy; NST, new systemic therapy.

Figure 13: Kaplan-Meier data for the individual transitions in REACH3

Abbreviations: BAT, best available therapy; NST, new systemic therapy.

B 11. Please explain the following sentence on page 96 of the CS: "As competing events are censored; it is not considered plausible to assume that the risk of failure or relapse would be higher with ruxolitinib compared with BAT". Also, on page 97, please explain why it is important that "the gamma model shows a similar shape for the ruxolitinib arm as is seen for the BAT arm".

After all competing events are censored, the observed incidence of events can be compared between arms directly. Competing risks analysis of both relapse of underlying malignancy (Figure 14) and non-relapse mortality (Figure 15) show lower incidence of events over time for ruxolitinib. As such, models that show higher rates of relapse of underlying malignancy or non-relapse mortality are considered implausible and this has been taken into account when selecting curves for the model base case.

Figure 14: Cumulative Incidence curve of Malignancy relapse/progression

Abbreviations: BID, twice daily; NA, not applicable.

Figure 15: Cumulative incidence curve of non-relapse mortality

Abbreviations: BID, twice daily; NA, not applicable.

Transitions to cGvHD have been assessed using independent models, with curve selection based of clinical input for extrapolations of BAT curves, and statistical fit. Preference was given to using the same parametric model in both arms, to allow for consistency in the way transitions probabilities evolve over time. However, the Gompertz model shows different patterns of survival between the ruxolitinib and BAT arms, so does not meet these criteria, and the generalised gamma model was preferred.

However, as acknowledged in Q B1, clinical experts indicated that it was not appropriate to use different incidence for cGVHD between ruxolitinib and BAT and the company base-case has been revised to use the same incidence of cGVHD between arm (see Q B1 for results).

Adverse events

B 12. Priority question. Please answer the following questions regarding the modelling of AEs.

a) Please clarify why REACH3 data have not been used to inform AEs.

As outlined in the CS and the response to A4, the focus of this submission is aGvHD. Chronic GvHD was included in the economic model as a subsequent event to capture the full trajectory of the disease. Treatments used for cGvHD are not the intervention or comparator in this analysis and have been excluded from the model. Given the limited impact of AEs in aGvHD, and that the same AEs would be applied in both arms of the model, the impact of including AEs in the cGvHD state is expected to be small.

b) Please clarify why some AEs have a disutility of 0.

Hypokalaemia, platelet count decreased, hypomagnesaemia, white blood cell count decreased, hyperglycaemia, and blood bilirubin increased are results of abnormal lab tests. Zero disutility was assumed for these abnormal lab tests, in line with TA642 (25) and TA949 (19).

c) The NICE methods indicate a preference for a multiplicative approach to disutilities, while the current model assumes these are additive. Please include both approaches in the model and give the user the option to choose which one will be used for the analyses.

An option of adopting multiplicative approach to disutilities have been included in the electronic model on the 'Utility data' sheet. Multiplier is calculated based on the baseline utility and utility decrements for each AE from Tolley 2013 (26) and Wehler 2018 (27). Scenario analysis using the multipliers shows very minimal impact of results, with the ICER falling from £25,161 to £25,144.

HRQoL

B 13. Priority question. Please answer the following questions regarding the modelling of HRQoL.

a) **Please explain why the data from REACH2 and 3 were pooled if from our understanding these are expected to be considered two different conditions/populations. For example, one answer from the individual validation calls with experts to the question "How do outcomes differ for de-novo cGvHD vs. patients who previously had aGvHD?" was the following: "These are very different groups, according to the clinical expert. Patients who have aGvHD and then develop cGvHD often have a higher degree of comorbidities with multiple infectious complications. They have worse performance status and are much sicker".**

Data from REACH2 and REACH3 were pooled to perform the utility analysis to allow a single model for utility with a single variance-covariance matrix to be constructed, however data from REACH2 was used to inform utility for the aGvHD states and data from REACH3 was used to inform utility for the cGvHD states.

Regarding whether using utility values from REACH3 for the cGVHD health state as a proxy for those entering the economic model (prior aGVHD) is appropriate, there were [redacted] observations of EQ-5D in patients with cGvHD in REACH2, and the mean utility value for these patients was [redacted]. In REACH-3, the mean utility for patients in the FF state was [redacted]. As such, utility values from REACH3 are expected to be generalisable to patients with cGvHD in the economic model. This was confirmed by clinical experts.

b) **Please clarify why a covariate for remaining in the failure-free health state beyond 4 cycles (112 days), and not some other cycle, was selected.**

Initial analysis of utility values did not include this covariate, however when this analysis was validated with clinical experts, they stated that the value for the FF state was too low for patients that remain in the state past the initial period in the model. Alternative approaches were explored, including using a continuous time in state covariate, however this was not applied as it would continue to extrapolate a benefit beyond the observed period which was not deemed plausible.

Cycle 4 was selected based on the observed data (CS Table 29, page 113). In cycles 1 to 3 the average utility values does not differ significantly from baseline. In cycle 4 there is an increase from baseline and then a further increase in cycle 5, after which the average utility remains stable.

c) **Please discuss the validity of the utility values observed in Table 29, and the link with the previous question b, given that the sample size is greatly reduced after the second and especially the third cycle. Please explain also why the number of observations increases in cycle 8+.**

The utility values in Table 29 of the CS are observed EQ-5D scores for patients remaining the failure-free state. An increase in utility over time is expected for these patients, as those that remain failure-free will be those who respond to treatment and do not require further treatment. This was validated with clinical experts, who stated that they expected the utility to increase over time, as observed in REACH2.

Observations for Cycle 8+ is the aggregated number of observations for all time points in Cycle 8 and beyond.

d) **In line with question a above, please discuss the validity of the utility values in Table 31 especially for the chronic health states given that these patients "have worse performance status and are much sicker". This does not seem to match with the values described in Table 31. For example, patients in NST (treated with BAT) can transition to cGvHD - failure-free (treated with BAT as well). A large improvement in the utility value seems irrational given that these patients are much sicker, and the treatment has not really changed. It is also difficult to understand why the utility values for NST are so different when having aGvHD or cGvHD, and why patients in aGvHD failure free transitioning to cGvHD in the first 4 cycles would also experience a large increase in utility. Please explain this as well.**

While there will be variation in utility values for patients who develop cGvHD, as outlined in part a), not all patients entering the cGvHD state will have progressive disease, and as outline above the observed utility values for these patients in

REACH2 are aligned with what is observed in REACH3. And therefore, using data from REACH-3 is appropriate, as validated by clinical expert.

e) **Please explain why on page 114, it is mentioned that experts "expected patients who remained in the failure-free state would have comparable quality of life to patients with cGvHD" when these patients who have aGvHD and then develop cGvHD often have a higher degree of comorbidities with multiple infectious complications and they have worse performance status and are much sicker.**

As stated in part a), not all patients who go on to develop cGvHD will have higher comorbidities and the observed utility values for patients with cGvHD in REACH2 are aligned with what is observed in REACH3.

f) **Please provide goodness-of-fit estimates for all models used to estimate utilities.**

Goodness-of-fit statistics are presented in Table 6.

Table 6: Goodness-of-fit statistics for utility models

Model	AIC	BIC
Model 1	–3215.7	–3149.1
Model 2	–3219.1	–3165.9
Model 3	–887.6	–827.7
Model 4	–891.9	–845.3

Abbreviations: AIC, Akaike information criteria; BIC, Bayesian information criteria.

g) **Please provide separate utility models for aGvHD and cGvHD utility values, and the option to use these in the model.**

Table 7 and Abbreviations: aGvHD, acute graft-versus-host-disease; AIC, Akaike information criteria; BIC, Bayesian information criteria; EQ-5D, EuroQol five-dimension; FF, failure-free; NST, new systemic therapy.

Table 8 present utility analysis for aGvHD and cGvHD separately. These analyses have been incorporated into the model and give results comparable to the jointly estimated models, with ICERs compared in Table 9.

Table 7: aGvHD utility models

	Model 1	Model 2	Model 3	Model 4
Baseline EQ-5D	[redacted]	[redacted]	[redacted]	[redacted]
FF, >4 cycles	[redacted]	[redacted]	[redacted]	[redacted]
NST	[redacted]	[redacted]	[redacted]	[redacted]
Relapse	[redacted]	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]
AIC	–579.0	430.9	–579.3	430.9
BIC	–538.9	465.3	–545.0	459.5

Abbreviations: aGvHD, acute graft-versus-host-disease; AIC, Akaike information criteria; BIC, Bayesian information criteria; EQ-5D, EuroQol five-dimension; FF, failure-free; NST, new systemic therapy.

Table 8: cGvHD utility models

	Model 1	Model 2	Model 3	Model 4
Baseline EQ-5D	[redacted]	[redacted]	[redacted]	[redacted]
NST	[redacted]	[redacted]	[redacted]	[redacted]
Relapse	[redacted]	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]
AIC	–3025.7	–1635.9	–3029.8	–1643.1
BIC	–2988.9	–1605.3	–2999.2	–1618.6

Abbreviations: AIC, Akaike information criteria; BIC, Bayesian information criteria; cGvHD, chronic graft-versus-host-disease; EQ-5D, EuroQol five-dimension; NST, new systemic therapy.

Table 9: Comparison of ICERs using jointly estimated and separate models for utility

	Joint model	Separate models
Model 1	£26,758	£26,969
Model 2	£26,857	£27,071
Model 3	£25,000	£24,979
Model 4	£25,161	£25,138

B 14. Priority question. Please compare the utility values in this appraisal with those in other relevant studies including TA949. Please consider for example Table 27 and discuss whether all studies where the source was REACH2 should have similar utilities.

Table 27 of the company submission identifies two prior economic models that have used data from REACH2 and REACH3 to inform utility analyses, which are appraisals of ruxolitinib for GvHD by CADTH and PBAC. The utility values applied are summarised in Table 10 and Table 11. The data used differs slightly from the data used in the present submission as it uses an earlier data cut, and in both cases EQ-5D-5L values have been used directly, rather than using values that have been mapped to the EQ-5D-3L.

Table 10: HSUVs applied in the CADTH analysis

Health state	aGvHD	cGvHD
Disease baseline	0.47	0.66
Week 4, overall responder	0.51	0.72
Week 4, non-responder	0.42	0.66
Week ≥12, overall responder	0.59	0.75
Week ≥12, non-responder	0.5	0.69

Abbreviations: aGvHD, acute graft-versus-host-disease; CADTH, Canadian Agency for Drugs and Technologies in Health; cGvHD, chronic graft-versus-host-disease; HSUV, health state utility value.

Table 11: HSUVs applied in the PBAC appraisal

Health state	aGvHD	cGvHD
Ruxolitinib responders	0.553	0.746
Ruxolitinib non-responders	0.441	0.687
BAT responders	0.553	0.695
BAT non-responders	0.441	0.636

Abbreviations: aGvHD, acute graft-versus-host-disease; BAT, best available therapy; cGvHD, chronic graft-versus-host-disease; HSUV, health state utility value; PBAC, Pharmaceutical Benefits Advisory Committee.

Despite some difference in the data, it is still expected that utility values would be comparable across analyses. Both prior analyses used a model based on response, rather than modelling FFS, and so direct comparison of values is difficult, however in both cases the values for responders (at Week 4 in the CADTH model) are close to the values used for failure-free in the first 4 cycles and values for non-responders are similar to those applied to the NST state. This is expected, as there will be a strong correlation between non-response and failure. Similarly to the present analysis, the values used in the CADTH appraisal include an element of time-dependency, with different values applied after Week 12. The value for responders after Week 12 is lower than that applied for the FF state after cycle 4, however this may be due to the use of the earlier data cut, which may have had fewer observations after Week 16. In the REACH 2 data used in this analysis, an improvement in utility after Week 12 is observed, however it is smaller than that seen at Week 16.

Utility values applied in TA949 have been marked as confidential, with the exception of the value applied for the failure state (0.479). This value was initially applied to both NST and relapse states in TA949, though it was calculated based on utility values for patients whose underlying disease has relapsed. This assumption was challenged during the appraisal and the value was only deemed plausible for the

relapse state. This value is lower than the observed value in relapsed patients in REACH2 and REACH3, and has been applied in the model base case.

B 15. Priority question. The SLR of the health-related quality of life studies included a total of 34 publications. The CS mentioned that 'a further 15 publications were included that are not relevant to the current decision problem, all of which were publications reporting on cGvHD patients alone'. As cGvHD is part of the model structure comprising of alternative health states, it is not clear why these 15 publications were considered not relevant for the decision problem, especially when data from REACH3 were pooled with data from REACH2 to estimate health state utilities. Please compare the health state utilities estimated for the company base case to the ones identified in the SLR and discuss which sources and scores would be representative of the current setting.

Across the de novo HRQoL & HSUV SLR and two SLR updates, a total of 34 publications were included. Of these, six publications reported on aGvHD patients alone, six publications reported separate data for aGvHD and cGvHD patients, seven publications reported on GvHD of unspecified type, and 15 publications reported on cGvHD patients alone.

The relevance of the non-cGvHD utility data (19 publications) to the current decision problem and NICE reference case is summarised in Section H.2.2 of Appendix H. The patient population being valued was completely aligned with the current decision problem (i.e. steroid-refractory aGvHD) in six publications (28-33). In five publications, the population being valued was aGvHD, but was not explicitly described as steroid-refractory, while in six publications, the population being valued was labelled as GvHD, but was not described as aGvHD or as steroid-refractory. In one of the remaining two publications, a utility value for aGvHD was estimated from proxy conditions such as hepatitis and non-infectious gastroenteritis (34), while in the other, a utility value was reported for a mixed population including 28.6% of patients with GvHD (35).

The EQ-5D questionnaire was used to describe health states in 11 out of 19 publications. Of the remaining eight publications, five elicited utility values using the TTO method, two employed the EQ-VAS only, and one mapped utility values from HRQoL data collected with the EORTC QLQ-C30 questionnaire. Health states were valued by patients in most publications, with the exception of one publication in which the identity of participants was unclear (34), and the five TTO studies, which recruited members of the general public (all of which involved participants in the UK) (36-40).

In the present submission, it was considered important to use utility data specific to steroid-refractory patients given prior evidence (for both aGvHD and cGvHD) that steroid-refractory patients have lower utility than steroid-responsive patients (41, 42). Overall, the aGvHD utility data best aligned with the current decision problem and NICE reference case are the EQ-5D-5L data for steroid-refractory aGvHD patients receiving ruxolitinib or BAT, collected within the REACH2 trial. This is because the EQ-5D instrument was employed, health states were valued by patients themselves, and the patient population was steroid-refractory, including some patients from the UK. Notably, a cross-sectional survey (Hamad 2021) also employed the EQ-5D-5L, involved the valuation of health states by patients with steroid-refractory aGvHD, and included some patients from the UK, together with others from Australia, Canada, France, and Switzerland (42). The utilities presented in this study (e.g. 0.53 for steroid-refractory aGvHD) were comparable to those derived from the REACH2 trial. The HOVON-113-MSC trial (30) also reported EQ-5D-5L data for steroid-refractory aGvHD patients, although the trial investigated a different intervention to REACH2 (MSC treatment), and no patients were from the UK. At baseline, mean EQ-5D score was 0.36, and 16% of patients had a negative EQ-5D value. This may reflect the fact that 85% of patients in HOVON-113-MSC had grade III or IV aGvHD, compared with only 64% in REACH2.

Regarding the 15 publications reporting cGvHD utility data alone (Table 12), seven reported on steroid-refractory cGvHD (28, 43-48). In another publication, only 35% of patients were steroid-refractory, though crucially, a utility value was reported for the

steroid-refractory subgroup (41). In the remaining seven publications, the population being valued was cGvHD, but was not explicitly described as steroid-refractory.

The EQ-5D questionnaire was used to describe health states in seven of 15 publications. Of the remaining eight publications, three did not specify the utility instrument, three reported VAS data only, one elicited utility values using the standard gamble method (49), and another mapped utility values from HRQoL data collected with the PROMIS-GH questionnaire (45). Health states were valued by patients in most publications, with the exception of the standard gamble study, which recruited physicians “familiar with transplantation outcomes” (49), and another study in which members of the UK general public valued health state vignettes using the EQ-5D-5L (48).

Overall, the cGvHD utility data best aligned with the current decision problem and NICE reference case are the EQ-5D-5L data for steroid-refractory cGvHD patients receiving ruxolitinib or BAT, collected within the REACH3 trial. This is because the EQ-5D instrument was employed, health states were valued by patients themselves, and the patient population was steroid-refractory, including some patients from the UK. Notably, a cross-sectional survey (Lachance 2021) also employed the EQ-5D-5L, involved the valuation of health states by patients with steroid-refractory cGvHD, and included some patients from the UK, together with others from Australia, Canada, France, and Switzerland (41). The utilities presented in this study (e.g. 0.69 for steroid-refractory cGvHD) were comparable to those derived from the REACH3 trial. By contrast, the utilities generated using the EQ-5D-5L in the UK vignette study (Williams 2023) were lower: 0.577, 0.336, and 0.172 for steroid-refractory cGvHD with complete response, partial response, and no response, respectively (48). It should be noted that these health states were valued by the general public rather than patients, and the authors speculate that “the low utility estimates are partly a reflection of the public’s perception of disease severity” and that “patients themselves may learn to cope and adjust over time” (48). Lastly, utility values cannot be compared between the REACH3 (ruxolitinib) trial and the ROCKstar (belumosudil) trial, since the latter are redacted in the publicly available submission documents for NICE TA949 (45). In addition, they would not be directly

comparable, given that EQ-5D values were mapped from PROMIS-GH data in the ROCKstar trial, and given all ROCKstar trial participants were from the USA (45).

***Table 12: Key characteristics of publications** from the HRQoL & HSUV SLRs reporting cGvHD utility data alone*

#	Short citation	Full citation	SLR	Utility instrument(s)	Population valuing health states	GvHD type	Steroid-refractory?	Study design	Intervention/ comparators (for GvHD)	Source of utility data
1	CADTH 2022 (SR0706-000)	Canadian Agency for Drugs and Technologies in Health (CADTH). SR0706-000. Ruxolitinib (Jakavi) for the treatment of chronic graft-versus-host disease in adults and pediatric patients aged 12 years and older who have inadequate response to corticosteroids or other systemic therapies. Available at: https://www.cadth.ca/ruxolitinib-0 (Last accessed 29 Mar 2024). 2022.	Second update (January 2024)	EQ-5D-5L	REACH3 trial patients (aged ≥12 years with moderate to severe SR-cGvHD)	Chronic	Yes	Economic model in HTA dossier	Ruxolitinib, BAT	Data from previously unpublished post-hoc analysis of REACH3 trial
2	Ong 2023	Ong JCM, Than H, Tripathi S, Gkitzia C, Wang X. A cost-effectiveness analysis of ruxolitinib versus best alternative therapy for patients with steroid-refractory chronic graft-versus-host disease aged > 12 years in Singapore. 2023;21(1).	Second update (January 2024)	EQ-5D-5L	REACH3 trial patients (aged ≥12 years with moderate to severe SR-cGvHD)	Chronic	Yes	Economic model	Ruxolitinib, BAT	Data from previously unpublished post-hoc analysis of REACH3 trial
3	Lee 2021	Lee S, Locatelli F, Ayuk FA, Zuckerman T, Fukushima K, Vallejo Llamas JC, et al. Patient-Reported Outcomes (PROs) Among Patients With Steroid-Refractory or -Dependent Chronic Graft-vs-Host Disease (cGVHD) Randomized to Ruxolitinib (RUX) vs Best Available Therapy (BAT). Blood. 2021;138(Supplement 1):3909.	Second update (January 2024)	EQ-5D-5L	REACH3 trial patients (aged ≥12 years with moderate to severe SR-cGvHD)	Chronic	Yes	Phase 3 REACH3 trial	Ruxolitinib, BAT	Data from study itself
4	Williams 2023	Williams E, Skinner L, Gruffydd E, Ecsy K, Sil A, Hudson R, et al. PCR207 A Vignette Study to Derive Health-Related Quality of Life Weights for Patients With Steroid Refractory Chronic Graft-Versus-Host Disease Receiving Third Line Therapy in the United Kingdom. Value in Health. 2023;26(12 Supplement):S489.	Second update (January 2024)	EQ-5D-5L, EQ-5D-VAS	General public in UK, aged ≥18 years, valuing health states in a utility elicitation exercise	Chronic	Yes	Utility elicitation exercise (vignette study)	None	Data from study itself
5	NICE 2024 (TA949)	National Institute for Health and Care Excellence (NICE). TA949. Belumosudil for treating chronic graft-versus-host disease after 2 or more systemic treatments in people 12 years and over. Available at: https://www.nice.org.uk/guidance/ta949 (last accessed 29 Mar 2024). 2024.	Second update (January 2024)	EQ-5D-3L mapped from PROMIS-GH data	ROCKstar trial patients (aged ≥12 years with moderate to severe cGvHD with ≥2 prior lines of systemic therapy)	Chronic	Yes	Economic model in HTA dossier	Belumosudil	PROMIS-GH data from the ROCKstar trial were mapped to EQ-5D-3L utility scores using a published algorithm
6	Lachance 2021	Lachance S, Hamad N, De Courcy J, Gibson G, Zuurman M et al. (2021) 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. 56: 83-84.	First update (September 2021)	EQ-5D-5L, EQ-5D-5L VAS	Patients with mild, moderate or severe cGvHD following allogeneic stem cell transplantation	Chronic	35%, with subgroup data presented for steroid-refractory patients	Observational study (cross-sectional survey)	None	Data from study itself

#	Short citation	Full citation	SLR	Utility instrument(s)	Population valuing health states	GvHD type	Steroid-refractory?	Study design	Intervention/ comparators (for GvHD)	Source of utility data
7	Lutz 2014	Lutz M, Kapp M, Einsele H, Grigoleit GU, Mielke S (2014) Improvement of quality of life in patients with steroid-refractory chronic graft-versus-host disease treated with the mTOR inhibitor everolimus. Clinical Transplantation. 28 (12): 1410-1415.	De novo (July 2019)	EQ-5D-3L (individual dimensions only), EQ-5D VAS	Patients with mild, moderate or severe steroid-refractory cGvHD	Chronic	Yes	Observational study (questionnaire study)	Everolimus	Data from study itself
8	Okamoto 2018	Okamoto S, Teshima T, Kosugi-Kanaya M, Kahata K, Kawashima N et al. (2018) Extracorporeal photopheresis with TC-V in Japanese patients with steroid-resistant chronic graft-versus-host disease. International journal of hematology. 108 (3): 298-305.	De novo (July 2019)	EQ-5D (CfB data only)	Patients with steroid-refractory cGvHD after allo-HSCT	Chronic	Yes	Interventional study (multicentre, uncontrolled, open-label study)	ECP	Data from study itself
9	Kanda 2023	Kanda Y, Usuki K, Inagaki M, Ohta A, Ogasawara Y, Obara N, et al. Decision analysis of allogeneic bone marrow transplantation versus immunosuppressive therapy for young adult patients with aplastic anemia. International Journal of Hematology. 2023;117(5):660-8.	Second update (January 2024)	Unclear, but utility values appear to be derived from VAS data	Patients who underwent allo-HSCT (some of which developed cGvHD)	Chronic	NR	Economic model	None	Kurosawa 2017 (see below)
10	Kurosawa 2017	Kurosawa S, Oshima K, Yamaguchi T, Yanagisawa A, Fukuda T et al. (2017) Quality of Life after Allogeneic Hematopoietic Cell Transplantation According to Affected Organ and Severity of Chronic Graft-versus-Host Disease. Biology of blood and marrow transplantation. 23 (10): 1749-1758.	De novo (July 2019)	VAS	Patients who underwent allo-HSCT (some of which developed cGvHD)	Chronic	NR	Observational study (cross-sectional survey)	None	Data from study itself
11	Kurosawa 2019	Kurosawa S, Yamaguchi T, Oshima K, Yanagisawa A, Fukuda T et al. (2019) Resolved versus Active Chronic Graft-versus-Host Disease: Impact on Post-Transplantation Quality of Life. Biology of Blood and Marrow Transplantation. 25 (9): 1851-1858.	De novo (July 2019)	VAS	Patients who underwent allo-HSCT (some of which developed cGvHD)	Chronic	NR	Observational study (cross-sectional survey)	None	Data from study itself
12	MSAC 2021	MSAC. (2021) 1651 – Integrated, closed-system, extracorporeal photopheresis systems for the treatment of chronic graft-versus-host disease (http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1651-public)	First update (September 2021)	NR	Patients with cGvHD	Chronic	NR	Economic model in HTA dossier	ECP, standard of care	De Waure 2015 and Crespo 2012 (see below)
13	De Waure 2015	De Waure C, Capri S, Veneziano MA, Specchia ML, Cadeddu C et al. (2015) Extracorporeal Photopheresis for Second-Line Treatment of Chronic Graft-versus-Host Diseases: Results from a Health Technology Assessment in Italy. Value in health. 18 (4): 457-466.	De novo (July 2019)	NR	Patients with cGvHD	Chronic	NR	Economic model	ECP, pentostatin, mycophenolate, imatinib	Crespo 2012 (see below)

#	Short citation	Full citation	SLR	Utility instrument(s)	Population valuing health states	GvHD type	Steroid-refractory?	Study design	Intervention/ comparators (for GvHD)	Source of utility data
14	Crespo 2012	Crespo C, Perez-Simon JA, Rodriguez JM, Sierra J, Brosa M (2012) Development of a Population-Based Cost-Effectiveness Model of Chronic Graft-Versus-Host Disease in Spain. Clinical Therapeutics 34 (8): 1774-1787.	De novo (July 2019)	NR	Patients with cGvHD	Chronic	NR	Economic model	ECP, rituximab, imatinib	Two review articles: Lee 2008 (50) and Pidala 2009 (51)
15	Lee 1997	Lee SJ, Kuntz KM, Horowitz MM, McGlave PB, Goldman JM, Sobocinski KA, et al. Unrelated Donor Bone Marrow Transplantation for Chronic Myelogenous Leukemia: A Decision Analysis Ann Intern M. 1997;127:1080-8.	Second update (January 2024)	Standard gamble	Physicians "familiar with transplantation outcomes" valuing health states in a utility elicitation exercise	Chronic	NR	Economic model, with utilities derived from a standard gamble utility elicitation exercise	None	Data from study itself

Abbreviations: allo-HSCT, allogeneic hematopoietic stem cell transplant; CfB, change from baseline; cGvHD, chronic graft-versus-host disease; BAT, best available therapy; ECP, extracorporeal photopheresis; EQ-5D, European Quality of Life Questionnaire – 5 Dimensions; EQ-5D-3L, European Quality of Life Questionnaire – 5 Dimensions – 3 Levels; EQ-5D-5L, European Quality of Life Questionnaire – 5 Dimensions – 5 Levels; GvHD, graft-versus-host disease; HRQoL, health related quality of life; HSUV, health state utility value; HTA, health technology assessment; NR, not reported; PROMIS-GH, Patient-Reported Outcomes Measurement Information System – Global Health; SLR, systematic literature review; SR-cGvHD, steroid-refractory chronic graft-versus-host disease; UK, United Kingdom; VAS, visual analog scale.

B 16. In the minutes of the advisory board meeting, it is mentioned that 'one clinical expert contacted after the advisory board expressed that he did not agree with the selection of the model at the advisory board. He explained that the average health state values were more appropriate, as the "failure-free, >4 cycles: [redacted]" and "cGvHD, failure-free: [redacted]" values were similar, and this is what is more clinically plausible. Therefore, a scenario was run with this utility model (and the rest of the models) to aid decision-making.' Please explain where these utility values come from and what scenario in the company's scenario analyses covers this additional analysis.

These are the mean utility values observed in these states in REACH2 and REACH3, and are applied in the scenario titled 'Average observed utility values'.

Costs and resource use

B 17. Priority question. Please confirm that the dosing regimen for ruxolitinib used in REACH2 (page 116 of the CS) is representative of UK clinical practice.

In line with clinical expert opinion, 10mg BID dosing as per the REACH2 trial is appropriate for the population of interest and reflective of UK clinical practice.

B 18. Priority question. On page 121 of the CS, it is mentioned that "Monitoring costs have been excluded from the model, as they are expected to be similar between arms, in line with TA949". Please clarify what types of costs should fall under this category and why they are expected to be similar. As TA949 concerned cGvHD patients, please explain why is it expected that monitoring options will be similar for aGvHD. Please clarify if tapering off ruxolitinib would require regular visits to the doctor (monitoring?) to decide the exact treatment dose and whether this should be included in the model. Please add the costs of these visits to the model.

Monitoring cost in aGvHD are not expected to be the same between aGvHD and cGvHD, rather they are expected to be the same between arms, as they were in the prior appraisal for cGvHD. Monitoring costs include haematologist visits and laboratory tests. Some elements of monitoring costs are captured in the

haematologist visits the FF and NST states, as there may be difference between arms where patients remain in the FF state longer for ruxolitinib.

In line with clinical opinion, tapering of ruxolitinib would require regular visits to the doctor every 2-4 weeks. Patients in both arms may undergo tapering of CNIs and no incremental cost associated with tapering is expected. Nevertheless, tapering costs for ruxolitinib have been incorporated into the base case to ensure any difference in costs is captured. Tapering guidelines indicated that tapering could start after Day 56 (Week 8) and should be completed by Week 24. Haematologist visits are already captured in Cycle 3 (Week 8-12). The cost of 2 additional haematologist visits has been applied in cycles 4 and 5 (Week 16-20 and Week 20-24) for the proportion of patients that tapered off ruxolitinib (31.6%). The impact on results is small, the base case ICER with tapering costs is £25,161, and this falls to £24,846 when tapering costs are excluded.

B 19. Priority question. Regarding Table 36 that presents the drug acquisition costs used in the economic analysis it was noted that for etanercept and Infliximab a different price per pack has been used in the economic model than the ones reported in Table 36 (and listed in the BNF prints provided with the references). Please provide the correct values and update the company's results if the prices in the model are incorrect. Also, for Infliximab the units per pack is set to 100 instead of 2 (cell G28 in the 'Cost data' sheet), whilst the mg per unit is set to 1 (cell H28), where it should be 120. Please explain if this is an error and make sure wastage costs and drug costs are calculated appropriately. Also, the 'per unit' column in the model (cells H19-H33) does not always match with the formulation sizes reported in Table 36. For etanercept, the model and Table 36 do match, but they are not consistent with the listing in BNF, which indicates that a unit is 25 mg. Please make sure the model input and inputs throughout Table 36 and in the BNF listings are in alignment and explain if changes had an impact on the company's base case results. Finally, please explain why the cost of mesenchymal stromal cells was informed by clinical opinion and not by a relevant database or publication.

We thank the EAG for highlighting this error. In Table 36 in the CS, formulation size of anti-thymocyte globulin should be 25 mg (52), formulation size of mycophenolate mofetil should be 250 mg (53) price per pack for mycophenolate mofetil should be £9.96 (53), price per pack for everolimus should be £445.50 (52), and price per pack for etanercept should be £643.50 (52). The updated table is presented in the appendix (Table 1).

The economic model is corrected to match the updated Table 36 in the CS accordingly. Specifically, in the 'Cost data' sheet, cell E24 is corrected to £9.96, cell H24 is corrected to 250, cell E25 is corrected to £362.55, precise data from eMIT (instead of rounded number) is updated in cell E23, cell E27 is corrected to £643.50, cell E28 is corrected to £755.32 with 2 vials per package and cell G28 and H28 are swapped. These corrections, alongside corrections to cGvHD costs detailed in response to question C5, lead to a small increase in the ICER compared with the CS, from £27,611 to £27,656.

The cost of mesenchymal stromal cells was informed by clinical opinion due to data absence from relevant database or publication.

B 20. Please clarify if any ruxolitinib dose reductions and temporary interruptions in patients with thrombocytopenia, neutropenia, or elevated total bilirubin after standard supportive therapy including growth factors, anti-infective therapies and transfusions (Table 2) have been included in the cost effectiveness model (and how).

The REACH2 trial has captured all ruxolitinib dose reductions and temporary interruptions in patients with thrombocytopenia, neutropenia, or elevated total bilirubin after standard supportive therapy including growth factors, anti-infective therapies and transfusions. This is captured in the model, as the dose of ruxolitinib has been calculated to match the total dose received in the trial. Explicitly modelling ruxolitinib dose reductions and temporary interruptions will double count the impact.

B 21. On page 26 of the CS, it is mentioned that treatment of aGvHD patients depends on the Grade of the disease. Please clarify if this distinction between disease Grade has been included in the cost effectiveness model (and how).

According to the NHS GvHD treatment guidelines, topical therapies (including hydrocortisone, eumovate, betnovate and dermovate) and optimisation of calcineurin inhibitors (tacrolimus or cyclosporine) and/or mycophenolate mofetil are the preferred approaches in the management of Grade I disease. Where patients present with Grade II-IV GvHD, systemic corticosteroids (methylprednisolone) are indicated first-line.

Grades are not distinguished in the cost effectiveness model because only patients with Grade II or above are included in the REACH2 trial and treatment of aGvHD patients does not depend on the Grade of the disease in REACH2. Although treatment of Grade I aGvHD is slightly different, Grade I acute GvHD is usually not considered as clinically important given its lack of effect on patient outcome (54), although it may progress to Grade II (please see our response to A1).

B 22. On page 121 of the CS, it is mentioned that a cost £11,786 was applied for patients who initiated treatment while in hospital, which was 14.9% of patients in REACH2. Please confirm if this percentage of patients is applied for both the BAT and ruxolitinib arms or differently.

This percentage of patients is applied for both the BAT and ruxolitinib arms.

Validation

B 23. Priority question. Please compare the cost-effectiveness results in this submission with those presented in Table 18 of the CS. Discuss the potential causes for discrepancies, especially in terms of life years (and QALYs), which appear to be quite substantial, when studies are based on REACH data as well.

Table 13 compares the QALYs for BAT and ruxolitinib in this analysis with those from previous cost-effectiveness analyses. The present analysis produces more QALYs for both the BAT and ruxolitinib arms than the previous analyses. All of the prior analyses use a model structure based around response, with OS extrapolated based on response status, rather than using FFS as an endpoint. As outlined in Section B.3.2.2 of the CS, a model based around FFS is considered more appropriate for this submission, though the difference in model structure alone would not explain the difference in QALYs. This is driven instead by differences in survival

data used. Since the publication of these models, additional follow-up from REACH2 has become available, with more data available on OS. In the previous models, OS data was only available up to 24 months, and modelled survival is lower than in this analysis. In the PBAC model, OS is ruxolitinib is 30% at year 2 and 20% at year 3, compared with 20% at year 2 and 12% at year 3 in the BAT arm. Survival in the CADTH report is presented by response status, with responder OS around 40% at year 2 and just under 30% at year 3. However, in the data cut used for this analysis, OS for the total ruxolitinib arm is 40% at year 2 and remains at 40% to the end of follow-up. This increase in survival drives the increase in QALYs in this analysis. While there may be some uncertainty in the extrapolation of OS in this analysis, as outlined in Appendix J, this does not translate into decision uncertainty and QALYs in all scenarios remain higher than those seen in previous analyses.

Table 13: Comparison of modelled outcomes with previous cost-effectiveness analyses

	PBAC model (33)	CADTH model (28)	Ong et al (47)	Current analysis
BAT QALYs	0.62	0.92	0.89	1.37
Ruxolitinib QALYs	0.84	1.07	1.04	[redacted]
Incremental	0.22	0.15	0.15	[redacted]

Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; PBAC, Pharmaceutical Benefits Advisory Committee; QALY, quality-adjusted life-year.

Priority question. On page 11 of the CS, it is mentioned that: "Patients with steroid-refractory acute GvHD (SR-aGvHD) have poor survival, with only 25% of patients alive 2 years after diagnosis, decreasing further to 10% at 4 years". In the model [redacted]% of BAT patients are alive at year 2, and [redacted]% of ruxolitinib patients. Please discuss the validity of the OS results predicted by the model.

The modelled OS for BAT is very similar to the observed data. KM survival at the end of follow-up was 30.6%, compared with [redacted]% in the model at the same time point. OS at the end of follow-up in the ruxolitinib arm of REACH2 was 38.7%, compared with [redacted]% in the economic model.

The figures quoted in the submission are from Westin 2011 (55) and Rashidi 2019 (56). Westin et al includes data on transplant performed between 1998 and 2002, and Rashidi et al uses data on transplant between 1990 and 2016, with 69% of transplants occurring before 2005, and some improvements in OS in this time may be expected. Extrapolations of OS were presented to clinicians at the advisory

board, with clinical experts agreeing that the extrapolations were reasonable, and the OS results predicted by the model are expected to be valid.

B 24. Priority question. Based on the short description in Table 18 of the CS, the structure of the model presented in the current submission seems quite different to those in previous studies. Please discuss what was the company's rationale for selecting a different model structure, especially when other models are based on REACH data as well.

While the model structure in Ong 2023, CADTH 2022 and PBAC 2022 are based on response rate, the health states of this submission are based on failure-free survival. The approach of using response rate in conjunction with FFS is criticised by NICE in TA949, with response removed from the model and the EAG suggested modelling failure events as separate health states (19).

As stated in the CS (Section B.3.2.2.2 Rationale for model structure), the approach taken was designed to address concerns that different failure mechanisms would be associated with different sets of costs and outcomes. Basing the model on FFS enables clinically important differences in costs and outcomes amongst the patients who experienced the clinically distinct events within FFS to be captured appropriately. The model structure used here also allows for explicit consideration of outcomes for patients that develop cGvHD, where multiple lines of therapy may be used and QoL and mortality can differ throughout the patient pathway. The approach was validated with clinicians and health economists. A similar model structure to this submission was used in James et al, 2019 where failure-free survival instead of response were used (57).

In comparison, the previous models based around response do not consider different mechanisms of failure, and their impact on costs, QoL and mortality. OS is extrapolated based on response, without time to next treatment or relapse being captured. Duration of response is considered and patients with a response can move to non-response, but relapse and time to NST are not explicitly included. Extrapolating outcomes based on FFS was considered more plausible than extrapolating based on response, as it explicitly considers the mechanism of failure when assessing costs, QoL and mortality.

Section C: Textual clarification and additional points

C 1. The PSA in the model takes several hours to run. The EAG would appreciate it if this could be more efficiently programmed. Also, please provide a rationale for choosing 5,000 iterations for the PSA.

The PSA requires the model trace to be recalculated, which adds additional time. It has not been possible to improve this in the time frame for response to CQs. 5,000 iterations are sufficient as the QALY and cost results from PSA are convergent to the base case results (Table 14). Figure 16 and Figure 17 show that cumulative average QALYs and costs are convergent at 5,000 iterations. Therefore, 5,000 iterations are sufficient for the PSA.

Table 14. Base-case results vs. PSA results (no severity multiplier)

	Total costs	Total QALYs	ICER per QALY
Base case			
BAT	£79,292	1.32	–
Ruxolitinib	[redacted]	[redacted]	£30,193
PSA			
BAT	£77,811	1.28	–
Ruxolitinib	[redacted]	[redacted]	£30,075

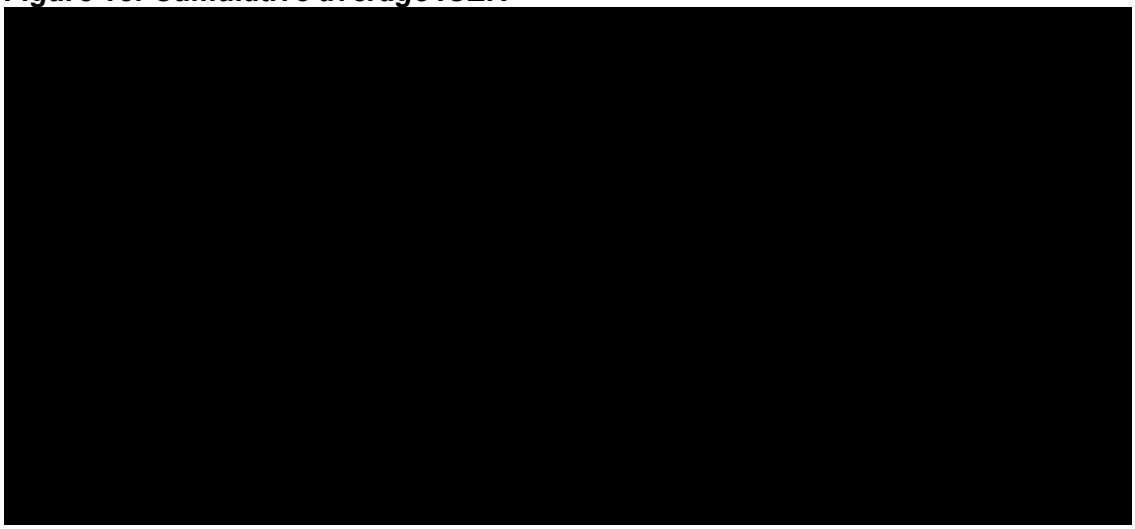
Abbreviations: BAT, best available therapy; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

Figure 16: Cumulative average incremental QALYs

Abbreviations: QALY, quality-adjusted life year.

Figure 17: Cumulative average costs

Figure 18: Cumulative average ICER



Abbreviations: ICER, incremental cost-effectiveness ratio.

C 2. Please check that the scenarios described and reported in Table 50 and Table 51 do not match completely as there are missing scenarios in both tables. Please amend them.

We thank the EAG for highlighting this error. 'Time horizon' was added to Table 50 and results for 'Joint models for post-failure outcomes' and 'Treatment waning after Year 3' were added to Table 51. All updated results are presented in the appendix.

C 3. Table 33 of the CS seems to present a mixture of the health state utility values for the health states of Relapse and Failure-free, 4 cycles, while for the

other health states it presents the coefficients of the model in Table 32, which are not the health state utility values. Please edit Table 33 to present the final health state utility values used in the model.

The values in Table 33 are the inputs used in the model, as these are the values that have confidence intervals. The values for failure-free, 4 cycles ins the constant terms from the utility model, and the value for relapse is the value taken from TA949. The remaining terms are the coefficients in the model for utility, and are relative to the failure-free, 4 cycles value.

C 4. The mean duration of treatment for ruxolitinib is reported to be [redacted] in Table 37, but in the model the mean duration of treatment is slightly different on the 'Rux costs' sheet. Please explain where in the model are the values in Table 37 of the CS for the alternative BAT treatments. Please explain why mesenchymal stromal cells with respective input is missing from Table 37.

We thank the EAG for highlighting this error. Cell L161 on the 'Rux costs' sheet should be '=SUM(L4:L157)/COUNT(L4:L157)' which results in [redacted] days.

C 5. Regarding Table 39:

a) Please explain why the percentage of incident cGvHD patients is described as the % of cGvHD 2L in the electronic model. Wouldn't these patients receive the 1L treatment as defined for cGvHD patients?

As demonstrated in Q4 c) steroids are the 1L treatment for both aGvHD and cGvHD. For patients who transition from aGvHD to cGvHD, they have received 1L treatment for cGvHD already. Therefore, treatment used in the failure-free cGvHD health state is viewed as a 2L treatment.

b) Everolimus is missing from this table but included in the electronic model. Please confirm which is the correct input.

We thank the EAG for highlighting this error. Everolimus has been added to Table 15.

Table 15: Cost of treatment for cGvHD

	cGvHD, treatment duration (weeks)	cGvHD, treatment dose per week	cGvHD, treatment cost	Incident cGvHD, %	CGvHD NST, %
Extracorporeal photopheresis	29.4	Twice per fortnight	£46,599.00	47.35%	35%
Mycophenolate mofetil	30.2	21,000 mg	£61.52	30.2%	17.21%
Sirolimus	39.8	7 mg	£803.61	5.99%	3.41%
Everolimus	39.8	10.5 mg	£4,139.29	4.35%	2.48%
Rituximab	6.4	500 mg	£3,087.89	5.17%	2.95%
Imatinib	32.1	2800 mg	£1,565.26	6.94%	3.95%
Belumosudil (list price)	40	1400 mg	£62,613.59	0.00%	35%
Total cost				**£22,636.12**	**£38,550.84**

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

c) For the column describing the % of cGvHD NST, the % do not match with the respective % included in the electronic model. Please explain which values are the right ones and make corrections accordingly.

We thank the EAG for highlighting this error. The values in the model were correct and are presented in Table 15.

C 6. Table 40 of the CS includes a cost for initial hospitalisation of £1,754.59. Please describe the source of this cost item (or method of computation) and indicate where this input is used in the electronic model.

Total cost for initial hospitalisation is calculated as the product of cost of initial hospitalisation and percentage of patients who require initial hospitalisation, where cost of initial hospitalisation is £11,786.25 and percentage of patients is 14.89%. The source of this cost item is detailed in the CS page 121 final paragraph and this input is used on the 'Cost data' sheet cell C55 and C56.

C 7. Table 44 of the CS includes multiple inconsistencies as compared to the model inputs used in the company's base case analysis. For instance, the parametric function for failure-free to cGvHD is not the same as the one in Table 24. The health state utilities seem also to be inconsistent with those reported in Tables 31 and 32. Finally, there are several inconsistencies in the drug acquisition costs. Please edit those and provide an updated Table 44.

We thank the EAG for highlighting this error. Table 44 has been corrected which now matches Table 24. All changes have been summarised in the appendix.

C 8. On page 92 of the CS, it is mentioned that in REACH2, 49 patients in the BAT arm (32%) crossed over to ruxolitinib at the end of the randomised treatment period and in REACH3, 61 patients in the BAT arm (37%) crossed over. Please clarify to what treatment patients crossed over in REACH3.

Patients in REACH3 crossed over to ruxolitinib.

C 9. Table 43 in the CS reports 1.43 QALYs for the comparator arm whereas this is 1.37 in Table 46. Please clarify which value is correct and amend the tables if needed.

We thank the EAG for highlighting this error. Table 43 in the CS has been updated in the after error correction and to reflect the updated base case analysis. Updates results are shown in Table 16.

Table 16: Summary of QALY shortfall analysis – Table 43 of the CS

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY shortfall
15.86	1.32	14.54	0.92

Abbreviations: QALY, quality-adjusted life year.

Section D: Additional questions

D 1. Regarding the modelling of competing events, DSU TSD19 states that "Competing risks analysis is used when there is a series of "competing" mutually exclusive events" and they cite the paper Putter et al. Tutorial in biostatistics: Competing risks and multi- state models. Statistics in Medicine. 2007;26:2389–430.

In that paper, it is explained that treating the events of the competing causes as censored observations will lead to a bias in the Kaplan–Meier estimate if one of the fundamental assumptions underlying the Kaplan–Meier estimator is violated: the assumption of independence of the time to event and the

censoring distributions. We understand that this is the approach that the company has taken, but we would like this to be clarified.

As it is usually impossible to know if this assumption can be made when competing risks are present, instead of the naïve KM approach, the so called cumulative incidence functions for each cause of failure should be derived. And these functions should be used for fitting parametric curves. So, we would like to ask the company that for all time-to-event curves that were explored in which competing risks were present, to provide the unbiased cumulative incidence functions, and provide parametric curves fitted to these functions.

The CEM is structured as a multi-state model, implemented in line with TSD19 (58) and Section 4 of the Putter tutorial (59) and accounts for competing risks.

For each transition, the cause-specific hazard function is derived by fitting models to survival data where events other than the event of interest are treated as censoring events. So, for example, when assessing the time to NST, the data used is the time to failure or incidence of cGvHD, and with patients who relapse, die or have incident cGvHD prior to NST being censored at that time. While it is correct to say that this KM curve cannot be used to directly extrapolate the proportion of patients that have transitioned NST at a given time point, it can be used to calculate the probability that a patient remaining in the FF state transitions to the NST state.

In Putter et al, the discretized version of the cause-specific hazard function for event k is defined as:

$$\widehat{\lambda_k}(t_j) = {}^{d_{kj}}\!/_{n_j}$$

Where d_{kj} is the number of patients failing from cause k at time t_j and n_j in the number of patients at risk at this time. This is what is represented in the cause-specific KM curves, presented in Figure 17 and 21 of the Company submission, and in Figure 11, Figure 12 and Figure 13 of this document. The unconditional probability of failing from cause k at time t_j, is the product of the hazard and the probability of being event-free at t_{j-1}, and is estimated as:

$$\widehat{p_k}(t_j) = \widehat{\lambda_k}(t_j)\hat{S}(t_{j-1})$$

Where $\hat{S}(t_{j-1})$ is the proportion of patients that remain at risk (i.e. have not experienced an event). This is equivalent to the way the total number of each type of event is calculated in the CEM. To calculate the number of NST events in each cycle, the proportion of patients that remain in the failure-free state is multiplied by the probability of an NST event, estimated from the cause-specific hazard function. The cumulative incidence function for cause k can then be defined as:

$$\widehat{I_k}(t) = \sum_{j:t_j \leq t} \widehat{p_k}(t_j)$$

This is the sum of the total number of events before time t and the CIF can be recreated in the model by summing up the total number of events in each cycle. For example, the CIF for NST for ruxolitinib and BAT can be recreated using the cumulative total of column T in the respective engine sheets, which shows the incident NST events in each cycle. This is shown in Figure 19. Note that this would not work for other events such as relapse or cGvHD using the data in columns U to X, as this includes transitions from other states.

Figure 19: CIF for NST estimated from the economic model

Abbreviations: CIF, cumulative incidence function; NST, new systemic therapy.

The CIF is a method to generate estimates of the cause-specific incidence in the presence of competing risk. Fitting survival models to this data, as the EAG suggests, will generate an appropriate estimate of the cause-specific survival over time, where the impact of competing risks is accounted for. A probability generated from these curves will give the marginal probability of an event, e.g. for the NST curve it would give the probability of an NST event occurring in that cycle for the total population, rather than the proportion of the population that remain failure-free. When used to generate transition probabilities for use in the model, it will underestimate the event rate, as the impact of competing risks will essentially be double counted as they have been directly incorporated into the model. This can be seen in Figure 20, which compares transition probabilities estimated from the CIF, to those used in the company submission. After time 0, the CIF probabilities sit below those used in the model.

Figure 20: Comparison of transitions to the NST state as estimated from the CIF and as per the Company Submission

Abbreviations: BAT, best available therapy; CIF, cumulative incidence function; NST, new systemic therapy.

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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 [ID6377]

Appendix to answers to EAG CQs – Corrections for company submission and updated results

30th July 2024

File name	Version	Contains confidential information	Date
ID6377 Ruxolitinib Appendix Corrections and updated results [REDACTED]	v1.0	Yes – CiC	30th July 2024

1. List of corrections made to the CS

Note: All corrections to the CS and results are outlined in red text.

B 19. Priority question. Regarding Table 36 that presents the drug acquisition costs used in the economic analysis it was noted that for etanercept and Infliximab a different price per pack has been used in the economic model than the ones reported in Table 36 (and listed in the BNF prints provided with the references). Please provide the correct values and update the company's results if the prices in the model are incorrect. Also, for Infliximab the units per pack is set to 100 instead of 2 (cell G28 in the 'Cost data' sheet), whilst the mg per unit is set to 1 (cell H28), where it should be 120. Please explain if this is an error and make sure wastage costs and drug costs are calculated appropriately. Also, the 'per unit' column in the model (cells H19-H33) does not always match with the formulation sizes reported in Table 36. For etanercept, the model and Table 36 do match, but they are not consistent with the listing in BNF, which indicates that a unit is 25 mg. Please make sure the model input and inputs throughout Table 36 and in the BNF listings are in alignment and explain if changes had an impact on the company's base case results. Finally, please explain why the cost of mesenchymal stromal cells was informed by clinical opinion and not by a relevant database or publication.

Table 36 of the CS is updated in Table 1. Please note we have left the reference numbers as they are in the original CS.

Table 1: Drug acquisition costs – Table 36 of the CS

Treatment	Formulation size	Price per pack	Pack size	Source
Ruxolitinib	10 mg	£2,856	56 tablets	BNF (113)
Ruxolitinib ([redacted] price)	10 mg	[redacted]	56 tablets	Novartis
Anti-thymocyte globulin	25 mg	£158.77	1 vial	BNF (113)
Extracorporeal photopheresis	N/A	£1,585 per procedure	N/A	TA949 (56)
Low-dose methotrexate	2.5 mg	£3.18	100 tablets	eMIT (112)
Mycophenolate mofetil	250 mg	£9.96	100 capsules	eMIT (112)
Everolimus	0.75 mg	£445.50	60 tablets	BNF (113)
Sirolimus	2 mg	£172.98	30 capsules	BNF (113)
Etanercept	50 mg	£643.50	4 pre-filled disposable syringes	BNF (113)
Infliximab	100 mg	£755.32	2 pre-filled disposable injection	BNF (113)

Treatment	Formulation size	Price per pack	Pack size	Source
Rituximab	1400 mg/11.7ml	£1,344.65	1	BNF (113)
Mesenchymal stromal cells	–	£12,000 per treatment course	N/A	Clinical opinion (9)

Abbreviations: BNF, British National Formulary; [redacted]; N/A, not applicable; TA, technology appraisal.

C 2. Please check that the scenarios described and reported in Table 50 and Table 51 do not match completely as there are missing scenarios in both tables. Please amend them.

In the electronic model on the 'Control' sheet, Column AT was inserted, and values are added to cell AT777 to AT804. Column AU and AV are swapped and AW and AX are swapped to match the order reported in Table 50 in the CS. The updated scenarios and results are presented in Table 2 and Table 3.

Table 2: Scenario analysis – Table 50 in the CS

Scenario	Details
Decision problem	
Time horizon = 20 years	To assess the impact of shorter time horizon on model outcomes
No discounting for costs or outcomes	To assess the impact of discounting on model outcomes
Clinical data	
Transition probabilities for the naïve analysis	Use models without adjustment for crossover (Section B.3.2.2)
Best fitting models	The choice of curves is guided AIC/BIC, rather than by clinical input (Section B.3.3.2)
Individual models for FF transitions	Separate models are fit for RUX and BAT for all transitions from the failure-free state (Section B.3.3.2). Models for transitions from FF are selected based on statistical fit and the remaining transitions are as per the base case.
Individual models, Clinician choice of curves	Aligned with the previous scenario, but with model selection informed by clinical input
Joint models for FF transitions	Joint models are fit for RUX and BAT for all transitions from the failure-free state (Section B.3.3.2). Models for transitions from FF are selected based on statistical fit and the remaining transitions are as per the base case.
Joint models, Clinician choice of curves	Aligned with the previous scenario, but with model selection informed by clinical input
Joint models for post-failure outcomes	Models including a treatment effect for RUX are fit for the post-failure states, excluding cGvHD states (Section B.3.3.2)
Treatment waning after Year 3	After Year 3, transition probabilities for ruxolitinib are set equal to BAT.
Utilities	

Scenario	Details
Average observed utility values	The average observed utility values from REACH2 and REACH3 are used for each health state
Mixed effects model	Alternative model specifications are used to generate utilities (Section B.3.4.5)
Mixed effects model, without relapse	
Fixed effects model	
cGvHD utility from TA949	cGvHD utility values taken from TA949 (56)
Costs and resource use	
ECP only for BAT	Assumes 100% of patients receive ECP as their first BAT treatment. There is no change in efficacy modelled.
BAT per clinician survey	One clinician conducted a survey of 27 transplant centres in the UK to assess the most common BAT treatments in UK clinical practice. After removing 6% the was assigned to BAT and 6.9% assigned to treatments not included in REACH2 the scenario uses the following treatment proportions: ECP, 73.7%; MMF, 9.5%; sirolimus, 4.8%; etanercept 6.6%; infliximab 3.9%; MSC, 1.5%.
ECP @ 60%	Increases the proportion of patients receiving ECP as their first-line treatment, reweighting the remaining treatment to retain the same proportional split as the model base case
ECP @ 80%	
BAT per REACH2	Using the proportion of patients receiving each treatment as was observed in REACH2
2L BAT = 1L BAT	The proportion of patients receiving each BAT treatment at 2L is equal to the proportion at 1L
No resource use costs	RUX increases survival, however the cost of providing care for patients with GvHD is high. In line with the NICE manual, a scenario is presented that removes the background costs.
cGvHD scenarios	
No costs for cGvHD	Much of the life-extension for RUX is spent in the cGvHD states, however these costs are not directly related to aGvHD and in line with the NICE manual scenarios removing these costs are considered.
No resource use for cGvHD	
BEL for 65% of 3L cGvHD	Increasing belumosudil use to 65% and assuming the remaining patients receive ECP
BEL only for 3L cGvHD	Increasing belumosudil use to 100%

Abbreviations: 1L, first-line; 2L, second-line; 3L, third-line; aGvHD, acute graft-versus-host disease; AIC, Akaike information criteria; BAT, best available therapy; BEL, belumosudil; BIC, Bayesian information criteria; cGvHD, chronic graft-versus-host disease; CS, company submission; ECP, extracorporeal photopheresis; FF, failure-free; MMF, mycophenolate mofetil; MSC, mesenchymal stromal cells; NICE, National Institute for Health and Care Excellence; RUX, ruxolitinib; TA, technology appraisal; UK, United Kingdom.

Table 3: Scenario analysis results – Table 51 in the CS

Scenario	Incremental costs	Incremental QALYs	ICER	ICER with severity modifier
Base-case	[redacted]	[redacted]	£29,815	£24,846
Decision problem				
Time horizon = 20 years	[redacted]	[redacted]	£39,570	£32,975
No discounting	[redacted]	[redacted]	£31,238	£26,032
Clinical data				
Transition probabilities for the naïve analysis	[redacted]	[redacted]	£30,996	£25,830
Best fitting models	[redacted]	[redacted]	£30,147	£25,123
Individual models for FF transitions	[redacted]	[redacted]	£28,935	£24,113
Individual models, Clinician choice of curves	[redacted]	[redacted]	£32,901	£27,417
Joint models for FF transitions	[redacted]	[redacted]	£27,245	£22,704
Joint models, Clinician choice of curves	[redacted]	[redacted]	£32,642	£27,202
Joint models for post-failure outcomes	[redacted]	[redacted]	£27,754	£23,129
Treatment waning after Year 3	[redacted]	[redacted]	£29,818	£24,849
Utilities				
Average observed utility values	[redacted]	[redacted]	£28,119	£23,433
Mixed effects model	[redacted]	[redacted]	£31,708	£26,423
Mixed effects model, without relapse	[redacted]	[redacted]	£31,824	£26,520
Fixed effects model	[redacted]	[redacted]	£29,624	£24,687
cGvHD utility from TA949	[redacted]	[redacted]	£31,540	£26,283
Costs and resource use				
ECP only for BAT	[redacted]	[redacted]	£22,316	£18,597
BAT per clinician survey	[redacted]	[redacted]	£26,835	£22,362
ECP @ 60%	[redacted]	[redacted]	£27,855	£23,212
ECP @ 80%	[redacted]	[redacted]	£25,085	£20,904
BAT per REACH2	[redacted]	[redacted]	£33,229	£27,691
2L BAT = 1L BAT	[redacted]	[redacted]	£28,064	£23,387
No resource use costs	[redacted]	[redacted]	Dominant	Dominant
cGvHD scenarios				
No costs for cGvHD	[redacted]	[redacted]	£1,642	£1,368

Scenario	Incremental costs	Incremental QALYs	ICER	ICER with severity modifier
No resource use for cGvHD	[redacted]	[redacted]	£8,032	£6,693
BEL for 65% of 3L cGvHD	[redacted]	[redacted]	£32,115	£26,762
BEL only for 3L cGvHD	[redacted]	[redacted]	£32,813	£27,344

Abbreviations: 1L, first-line; 2L, second-line; 3L, third-line; aGvHD, acute graft-versus-host disease; AIC, Akaike information criteria; BAT, best available therapy; BEL, belumosudil; BIC, Bayesian information criteria; cGvHD, chronic graft-versus-host disease; CS, company submission; ECP, extracorporeal photopheresis; FF, failure-free; ICER, incremental cost-effectiveness ratio; MMF, mycophenolate mofetil; MSC, mesenchymal stromal cells; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life year; RUX, ruxolitinib; TA, technology appraisal; UK, United Kingdom.

C 5. Regarding Table 39:

b) Everolimus is missing from this table but included in the electronic model. Please confirm which is the correct input.

c) For the column describing the % of cGvHD NST, the % do not match with the respective % included in the electronic model. Please explain which values are the right ones and make corrections accordingly

Table 39 of the CS is updated in Table 4.

Table 4: Cost of treatment for cGvHD – Table 39 of the CS

	cGvHD, treatment duration (weeks)	cGvHD, treatment dose per week	cGvHD, treatment cost	Incident cGvHD, %	CGvHD NST, %
Extracorporeal photopheresis	29.4	Twice per fortnight	£46,599.00	47.35%	35%
Mycophenolate mofetil	30.2	21,000 mg	£61.52	30.2%	17.21%
Sirolimus	39.8	7 mg	£803.61	5.99%	3.41%
Everolimus	39.8	10.5 mg	£4,139.29	4.35%	2.48%
Rituximab	6.4	500 mg	£3,087.89	5.17%	2.95%
Imatinib	32.1	2800 mg	£1,565.26	6.94%	3.95%
Belumosudil (list price)	40	1400 mg	£62,613.59	0.00%	35%
Total cost				**£22,636.12**	**£38,550.84**

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

C 7. Table 44 of the CS includes multiple inconsistencies as compared to the model inputs used in the company's base case analysis. For instance, the parametric function for failure-free to cGvHD is not the same as the one in Table 24. The health state utilities seem also to be inconsistent with those reported in Tables 31 and 32. Finally, there are several inconsistencies in the drug acquisition costs. Please edit those and provide an updated Table 44.

Table 44 of the CS is updated in Table 5.

Table 5: Summary of model inputs applied to model – Table 44 of the CS

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
General parameters			
Discount rate, costs	3.5%	Fixed	B.3.2.3
Discount rate, outcomes	3.5%	Fixed	
Time horizon	Lifetime	Fixed	
Baseline age	49.5	Fixed	B.3.3.1
% female	41%	Fixed	
Body weight (kg)	66.9	Fixed	
Transition probabilities			
Failure-free to NST	Gompertz	Multivariate normal distribution	B.3.3.2
Failure-free to relapse	Generalised gamma		
Failure-free to cGvHD	Generalised gamma		
Failure-free to death	Generalised gamma		
NST to relapse	Exponential		
NST to cGvHD	Exponential		
NST to Death	Generalised gamma		
Relapse to death	Log-logistic		
cGvHD to NST	Gompertz		
cGvHD to relapse	Exponential		
cGvHD to death	Exponential		
cGvHD, NST to relapse	Exponential		
cGvHD, NST to death	Exponential		
cGvHD, Relapse to death	Log-normal		
Background mortality			
Background mortality	England and Wales lifetables	Fixed	B.3.3.4
Utility values			
Health state utilities			
Failure free, ≤4 cycles	[redacted]	Multivariate normal distribution	B.3.4.5**Error! Reference source not found.**
Failure free, >4 cycles	[redacted]		
NST	[redacted]		
Relapse	[redacted]	Beta distribution	
cGvHD, failure-free	[redacted]	Multivariate normal distribution	
cGvHD, NST	[redacted]		
cGvHD, relapse	[redacted]	Beta distribution	
AE disutilities			
Anaemia	–0.090	+/–20%	Table 28

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Thrombocytopenia	–0.110		
Cytomegalovirus infection reactivation	–0.220		
Neutropenia	–0.160		
Oedema peripheral	–0.195		
Hypokalaemia	0.000		
Pyrexia	–0.195		
Platelet count decreased	–0.000		
Nausea	–0.200		
Vomiting	–0.200		
Diarrhoea	–0.200		
Hypomagnesaemia	–0.000		
Hypertension	–0.020		
White blood cell count decreased	–0.000		
Abdominal pain	–0.200		
Acute kidney injury	–0.195		
Neutrophil count decreased	–0.160		
Pneumonia	–0.195		
Sepsis	–0.195		
Alanine aminotransferase increased	–0.050		
Urinary tract infection	–0.220		
Hypocalcaemia	–0.000		
Hypophosphataemia	–0.000		
Hyperglycaemia	–0.000		
Blood bilirubin increased	–0.000		
Costs			
Drug acquisition costs			
Ruxolitinib	£2856	Fixed	B.3.5.1
Anti-thymocyte globulin	£158.77		
Extracorporeal photopheresis	£1585 per procedure		
Low-dose methotrexate	£3.18		
Mycophenolate mofetil	£9.96		
Everolimus	£362.55		
Sirolimus	£172.98		
Etanercept	£643.50		
Infliximab	£755.32		
Rituximab	£1344.65		
Mesenchymal stromal cells	£12,000 per treatment course		
Resource use costs			
Initial hospitalisation	£1,754.59	+/–20%	B.3.5.2

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Failure-free, cycles 1–3	£1,407.80		
Failure-free, cycles 4+	£1,006.16		
NST	£1,407.80		
Relapse	£2,719.46		
cGvHD failure-free	£1,782.44		
cGvHD NST	£1,782.44		
cGvHD relapse	£2,719.46		
Adverse events cost			
Anaemia	£410.69	+/–20%	B.3.5.3
Thrombocytopenia	£427.06		
Cytomegalovirus infection reactivation	£1,955.82		
Neutropenia	£377.81		
Oedema peripheral	£576.05		
Hypokalaemia	£372.13		
Pyrexia	£576.05		
Platelet count decreased	£2,055.69		
Nausea	£163.36		
Vomiting	£163.36		
Diarrhoea	£163.36		
Hypomagnesaemia	£543.55		
Hypertension	£574.37		
White blood cell count decreased	£163.36		
Abdominal pain	£576.05		
Acute kidney injury	£880.67		
Neutrophil count decreased	£372.13		
Pneumonia	£576.05		
Sepsis	£311.58		
Alanine aminotransferase increased	£567.09		
Urinary tract infection	£1,955.82		
Hypocalcaemia	£372.13		
Hypophosphataemia	£372.13		
Hyperglycaemia	£428.03		
Blood bilirubin increased	£0.00		

Abbreviations: AE, adverse event; cGvHD, chronic graft-versus-host-disease; CI, confidence interval; CS, company submission; NST, new systemic therapy.

C 9. Table 43 in the CS reports 1.43 QALYs for the comparator arm whereas this is 1.37 in Table 46. Please clarify which value is correct and amend the tables if needed.

Table 43 of the CS is updated in Table 6.

Table 6: Summary of QALY shortfall analysis – Table 43 of the CS

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY shortfall
15.86	1.32	14.54	0.92

Abbreviations: CS, company submission; QALY, quality-adjusted life year.

2. Updated cost-effectiveness results

Drug costs in the economic model have been updated in line with the responses to questions B19 and C5, which impacts results of the cost-effectiveness analyses. Updated results from the company submission are presented below. The correction led to a small increase in the ICER, driven by a small increase in incremental costs. There are no changes in QALYs for either arm. Table 7 and Table 8 present the results of the original CS, results after error corrections addressed by the EAG, and the results of the updated base case. The updated base case analysis uses the same rate of cGvHD in both arms of the model and includes additional monitoring for tapering of ruxolitinib.

Table 7: Base-case results (deterministic), with [redacted] price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	ICER with severity modifier (£/QALY)
Original CS								
BAT	£79,632	2.74	1.37	–	–	–	–	–
Ruxolitinib ([redacted] price)	[redacted]	3.77	[redacted]	[redacted]	1.02	[redacted]	£33,133	£27,611
With error corrections addressed by the EAG								
BAT	£79,744	2.74	1.37	–	–	–	–	–
Ruxolitinib ([redacted] price)	[redacted]	3.77	[redacted]	[redacted]	1.02	[redacted]	£33,188	£27,656
Updated base case								
BAT	£79,292	2.59	1.32	–	–	–	–	–
Ruxolitinib ([redacted] price)	[redacted]	3.83	[redacted]	[redacted]	1.24	[redacted]	£30,193	£25,161

Abbreviations: BAT, best available therapy; [redacted] ICER, incremental cost-effectiveness ratio; LYG, life year gained; QALY, quality-adjusted life year.

Table 8: Net health benefit, with [redacted] price

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000	NHB at £20,000 with severity modifier	NHB at £30,000 with severity modifier
Original CS								
BAT	£79,744	1.37	–	–	–	–	–	–
Ruxolitinib ([redacted] price)	[redacted]	[redacted]	[redacted]	[redacted]	–0.38	–0.06	–0.27	0.05
With error corrections addressed by the EAG								
BAT	£79,744	1.37	–	–	–	–	–	–
Ruxolitinib ([redacted] price)	[redacted]	[redacted]	[redacted]	[redacted]	–0.38	–0.06	–0.27	0.05
Updated base case								
BAT	£79,292	1.32	–	–	–	–	–	–
Ruxolitinib ([redacted] price)	[redacted]	1.98	[redacted]	[redacted]	-0.34	0.00	-0.21	0.13

Abbreviations: BAT, best available therapy; [redacted] ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALY, quality-adjusted life year.

Results of the PSA using the updated base case are shown in Table 9, Figure 1 and Figure 2. Results are consistent with the CS.

Table 9: PSA results (ruxolitinib [redacted] price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	ICER with severity modifier (£/QALY)
BAT	£77,811	1.28	–	–	–	–
Ruxolitinib ([redacted] price)	[redacted]	[redacted]	[redacted]	[redacted]	£30,075	£25,063

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.

Figure 1: Cost-effectiveness plane (ruxolitinib [redacted] price, with modifier)

[redacted]

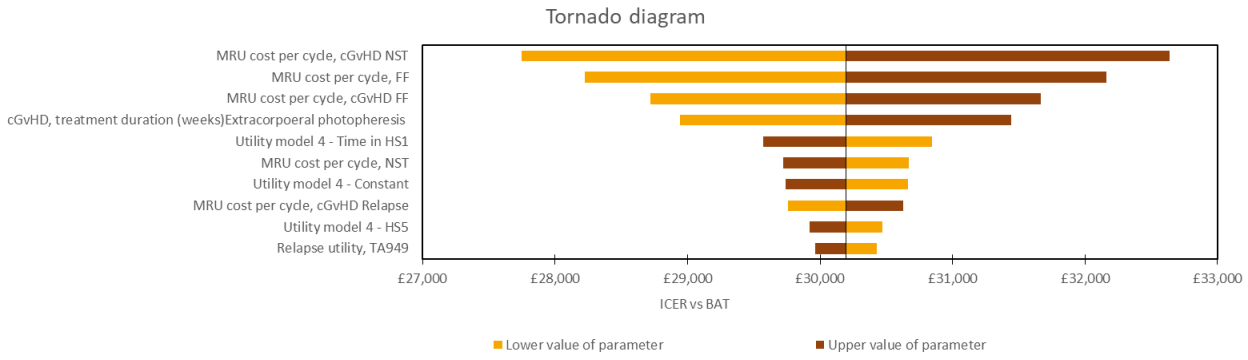
Abbreviations: BAT, best available therapy; [redacted] QALY, quality-adjusted life year.

Figure 2: Cost-effectiveness acceptability curve (ruxolitinib [redacted] price, with modifier)

Abbreviations: BAT, best available therapy; [redacted]

Results of the DSA are presented in **Error! Reference source not found.** and Table 10. Results are consistent with the CS.

Figure 3: Tornado diagram



Abbreviations: BAT, best available therapy; cGvHD, chronic graft-versus-host-disease; HS, health state; FF, failure-free; ICER, incremental cost-effectiveness ratio; MRU, medical resource use; NST, new systemic therapy; RUX, ruxolitinib; TA, technology appraisal.

Table 10: Outcomes of the DSA (with and without severity modifier)

Parameter	With severity modifier		Without severity modifier	
	ICER at lower value of parameter	ICER at upper value of parameter	ICER at lower value of parameter	ICER at upper value of parameter
MRU cost per cycle, cGvHD NST	£27,746	£32,640	£23,122	£27,200
MRU cost per cycle, FF	£28,223	£32,164	£23,519	£26,803

Parameter	With severity modifier		Without severity modifier	
	ICER at lower value of parameter	ICER at upper value of parameter	ICER at lower value of parameter	ICER at upper value of parameter
MRU cost per cycle, cGvHD FF	£28,719	£31,667	£23,933	£26,389
cGvHD, treatment duration (weeks) Extracorporeal photopheresis	£28,945	£31,441	£24,121	£26,201
Utility model 4 - Time in HS1	£30,844	£29,570	£25,703	£24,642
MRU cost per cycle, NST	£30,667	£29,719	£25,556	£24,766
Utility model 4 - Constant	£30,663	£29,738	£25,552	£24,782
MRU cost per cycle, cGvHD Relapse	£29,758	£30,629	£24,798	£25,524
Utility model 4 - HS5	£30,473	£29,918	£25,394	£24,932
Relapse utility, TA949	£30,428	£29,962	£25,357	£24,968

Abbreviations: cGvHD, chronic graft-versus-host-disease; DSA, deterministic sensitivity analysis; ECP, extracorporeal photopheresis; FF, failure-free; HS, health state; ICER, incremental cost-effectiveness ratio; MRU, medical resource use; NST, new systemic therapy; TA, technology appraisal.

Results of the scenario analyses are presented in Table 11. Corrections have been made to some of the clinical data scenarios, as the model was not updating selections correctly. However, these changes to not impact the conclusions of the scenario analyses, with ruxolitinib remaining cost-effective in all of the clinical data scenarios. The remaining scenarios are consistent with those presented CS.

Table 11: Scenario analysis results

Scenario	Incremental costs	Incremental QALYs	ICER	ICER with severity modifier
Base-case	[redacted]	[redacted]	£30,193	£25,161
Decision problem				
Time horizon = 20 years	[redacted]	[redacted]	£40,087	£33,406
No discounting	[redacted]	[redacted]	£31,549	£26,291
Clinical data				
Transition probabilities for the naïve analysis	[redacted]	[redacted]	£31,299	£26,082
Best fitting models	[redacted]	[redacted]	£30,531	£25,443
Individual models for FF transitions	[redacted]	[redacted]	£29,530	£24,608
Individual models, Clinician choice of curves	[redacted]	[redacted]	£33,484	£27,904
Joint models for FF transitions	[redacted]	[redacted]	£27,641	£23,034

Scenario	Incremental costs	Incremental QALYs	ICER	ICER with severity modifier
Joint models, Clinician choice of curves	[redacted]	[redacted]	£33,044	£27,537
Joint models for post-failure outcomes	[redacted]	[redacted]	£28,161	£23,468
Treatment waning after Year 3	[redacted]	[redacted]	£30,198	£25,165
Utilities				
Average observed utility values	[redacted]	[redacted]	£28,476	£23,730
Mixed effects model	[redacted]	[redacted]	£32,110	£26,758
Mixed effects model, without relapse	[redacted]	[redacted]	£32,228	£26,857
Fixed effects model	[redacted]	[redacted]	£30,000	£25,000
cGvHD utility from TA949	[redacted]	[redacted]	£31,940	£26,617
Costs and resource use				
ECP only for BAT	[redacted]	[redacted]	£22,695	£18,912
BAT per clinician survey	[redacted]	[redacted]	£27,213	£22,678
ECP @ 60%	[redacted]	[redacted]	£28,233	£23,528
ECP @ 80%	[redacted]	[redacted]	£25,464	£21,220
BAT per REACH2	[redacted]	[redacted]	£33,608	£28,006
2L BAT = 1L BAT	[redacted]	[redacted]	£28,443	£23,702
No resource use costs	[redacted]	[redacted]	£144	£120
cGvHD scenarios				
No costs for cGvHD	[redacted]	[redacted]	£2,020	£1,684
No resource use for cGvHD	[redacted]	[redacted]	£8,411	£7,009
BEL for 65% of 3L cGvHD	[redacted]	[redacted]	£32,493	£27,078
BEL only for 3L cGvHD	[redacted]	[redacted]	£33,192	£27,660

Abbreviations: 1L, first-line; 2L, second-line; 3L, third-line; BAT, best available therapy; BEL, belumosudil; cGvHD, chronic graft-versus-host disease; ECP, extracorporeal photopheresis; FF, failure-free; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TA, technology appraisal.

Additional scenario analysis

Additional scenario analysis to accompany the response to CQs is presented below.

Table 12 summarises the different scenarios, with results presented in Table 13.

Table 12: Summary of additional scenarios

Scenario	Approach	Relevant CQ
Treatment waning from Year 2	Transition probabilities for ruxolitinib are equal to those for BAT after Year 2	B3
No additional monitoring for tapering of ruxolitinib	Additional haematologist visits for tapering are excluded	B18
Separate utility analyses, Model 1	Separate models are used to assess utility for aGvHD and cGvHD health states	B13
Separate utility analyses, Model 2		
Separate utility analyses, Model 3		
Separate utility analyses, Model 4		
Multipliers for AE disutilities	The disutility associated with AEs is based on multipliers, rather than absolute disutilities.	B12

Abbreviations: AE, adverse event; aGvHD, acute graft-versus-host disease; BAT, best available therapy; cGvHD, chronic graft-versus-host disease; CQ, clarification question.

Table 13: Results of additional scenarios

Scenario	Incremental costs	Incremental QALYs	ICER	ICER with severity modifier
Base case	[redacted]	[redacted]	£30,193	£25,161
No additional monitoring for tapering of ruxolitinib	[redacted]	[redacted]	£29,815	£24,846
Treatment waning from Year 2	[redacted]	[redacted]	£30,196	£25,164
Separate utility analyses, Model 1	[redacted]	[redacted]	£32,363	£26,969
Separate utility analyses, Model 2	[redacted]	[redacted]	£32,485	£27,071
Separate utility analyses, Model 3	[redacted]	[redacted]	£29,975	£24,979
Separate utility analyses, Model 4	[redacted]	[redacted]	£30,165	£25,138
Multipliers for AE disutilities	[redacted]	[redacted]	£30,173	£25,144

Abbreviations: AE, adverse event; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

NICE 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 [ID6377]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Anthony Nolan and Leukaemia Care
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Anthony Nolan is a UK stem cell transplant charity with 50 years of expertise in uniting science and people to push the boundaries of what can be achieved for blood cancer and blood disorder patients. Our world-leading stem cell register matches potential donors to patients in need of transplants. We carry out cell and gene therapy research to increase transplant success and supports patients through their transplant journeys. Anthony Nolan helps four people in need of a transplant a day, giving more people a second chance at life. We are funded by a combination of income sources as detailed in our annual report. In this submission, we are representing the views and experiences of stem cell transplant recipients, who have experienced acute Graft vs Host Disease (GvHD). Leukaemia Care is the UK's leading leukaemia charity, founded in 1969. We are dedicated to ensuring that anyone affected by blood cancer receives the right information, advice and support. Approximately 85-90% of our income comes from fundraising activities – such as legacies, community events, marathons etc. Leukaemia Care also receives funding from a wide range of pharmaceutical companies, accounting for 18.82% of Leukaemia Care's annual income in 2022.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the	**Anthony Nolan** **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.

comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	**Pfizer:** We received **£300** to attend an advisory board to develop principles of care to inform a Blood Cancer Patient Charter. **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. **Leukaemia Care**Pharma funding (all 2022, the latest available): Pfizer: £20,000 for core funding and £23,135 for the AML Testing Project
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	Anthony Nolan directly interviewed patient and family members with experience of acute GvHD. We have also used insights from our patient helpline, online forum and engagement with patients and families through networks such as the Anthony Nolan Patients and Families Network and our Policy Insights Panel.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	**Living with acute GvHD** Acute graft-versus-host disease (GvHD) is a very difficult condition to live with. As it generally occurs within the first few weeks and months after a donor stem cell transplant, it adds to what is already a physically and emotionally difficult time for patients, their family members and carers. It can affect any part of the body and commonly impacts the lungs, skin, gut, mouth, liver, genital area, joints and muscles. Acute GvHD causes physical symptoms that are very distressing and difficult to manage. For example, acute GvHD that affects the skin can cover large portions of the body and make contact against clothes, sheets and furniture painful. Patients are often given topical creams to try to help ease the symptoms, which need to be reapplied frequently, and often it is a family member/carer having to do this as the patient is too unwell to do so. A patient said, "*I had to have lotions applied gently from head to toe every hour during the night, which required almost full-time nursing. At that point I was using around 38 different medications."* Another common manifestation of GvHD is in the mouth and gut. Patients often struggle to swallow due to symptoms such as mouth ulcers and this can cause extreme weight loss, in severe cases a feeding tube might be needed. This is also distressing to family members. One patient noted that their mouth became so ulcerated they could not eat or drink at all, resulting in hospital admission. This impact on their ability to eat and drink means patients are often very weak and are unable to provide their body with the nutrients it needs to recover. It also makes it even harder to follow a neutropenic diet which is key to avoiding infection after transplant. Also distressing for patients is that acute GvHD can necessitate frequent hospital admissions due to infection. Sepsis as a complication of acute GvHD and its treatment can be life threatening and this makes avoiding any source of infection a key priority for patients and families. This has the additional toll of impacting their mental and social wellbeing, adding to the prolonged periods of isolation experienced during and after their initial transplant. One patient Anthony Nolan interviewed had contracted sepsis 9 times, often as a direct result of acute GvHD. These infections required extended hospital stays including one which lasted five weeks at their transplant centre a significant distance from home and another spell of 10 weeks in a local hospital. **Mental Health Impact**

	The mental health impact of experiencing acute GvHD after a transplant, and the uncertainty of whether or not it will ever resolve, is very detrimental to patients. *"You realise how stressful it was in retrospect. It's taken several years afterwards to recover from the stress and the trauma."* The symptoms of acute GvHD can be life threatening, which results in anxiety and stress not only for patients but also their friends and families. Anthony Nolan has spoken to patients who noted that there is a psychological impact of thinking they will be back at full health after their transplant only to experience GvHD which is very demoralising after the intensity of the transplant itself. "*The transplant had gone very smoothly, so to see my partner then have acute GvHD was both worrying and stressful. We did everything we could to try and keep him out of hospital."* Due to the variety of acute GvHD complications, patients are often receive care from across different specialities, who many not always be equipped to meet their unique needs as post-transplant patients, for example dermatologists, gastroenterologists, dieticians and psychologists can all contribute to the care of acute GvHD. The burden of self-advocating and navigating the complex medical system often falls on patients and their families which adds additional stress during their recovery period. **Financial Impact** The negative financial impact of acute GvHD can be significant for patients and carers, for example due to having to wash clothes more frequently, purchase topical creams, and travel in a private vehicle to hospital appointments for GvHD treatments to avoid infection. In addition, if a patient has a non-cancer indication for transplant they may have to pay a prescription charge for medication. Anthony Nolan estimates that stem cell transplant patients on average live 32.4 miles from their transplant centre, therefore travelling 64.8 miles to and from specialist hospital appointments. As ECP is not offered at every transplant centre, costs may be even higher for patients with GvHD. These long distances result in a large cost burden, of at least £30 per round trip which can increase greatly depending on where a patient lives.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	The treatment currently available, including steroids and extracorporeal photopheresis (ECP), have several drawbacks. Topical steroids and creams are very time and labour intensive to apply as mentioned above and are mostly only effective for mild cases of skin GvHD. Many patients would prefer not to overuse systemic steroids as they contribute to a range of side effects, which adds to existing early post-transplant issues, and combined can be very debilitating for patients. This includes immunosuppression which increases the likelihood of bacterial, viral or fungal infections and can result in hospitalisation. Additionally, steroid myopathy and weight gain can cause mobility problems for patients and delay recovery post-transplant. Patients also worry about the increased risk of osteoporosis and diabetes from prolonged steroid use. Anthony Nolan interviewed patients that remarked on the side effects of high-dose steroids, whether that was indigestion, dizziness and changes in blood pressure, swings in body temperature and the long tapering off from the high doses. These treatments initially made them feel a lot worse and none said they would favour having to go through the same experience again. "*I was on so many different medications, at one point the steroids I was taking caused cataracts and I had to have surgery on my eyes, and because I had become hyperglycaemic I had to take insulin which took another year to be weaned off from".* ECP requires travel to and from the ECP centre, this can be very costly and is an added burden for highly immunocompromised patients. Due to the increased risk of infection after a transplant and diminished immune system, avoiding the hospital or any unnecessary travel is extremely important. Often patients will need to take a private vehicle to appointments as public transport is not advised. This means they often rely on carers to support them to attend appointments, as adult patients are too weak to drive themselves to receive treatment. In addition to the travel burden, ECP requires patients to spend hours on the machine receiving the treatment intravenously. This can have a significant effect on patients' ability to have a normal life, including working and having a social life. Blood clots often cause ECP treatment to be disrupted and are also inherently dangerous for patients.
8. Is there an unmet need for patients with this condition?	Yes. There is a significant unmet need especially for acute GVHD that does not respond to available treatments; and for effective treatments that alleviate the time, cost and mental health burden to patients and families.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Patients and family members are desperate for additional treatment options for acute GvHD that doesn't respond to existing treatments. Many patients and families are very aware that this product is available as standard of care in other countries and that some patients were able to access it for a limited period during the height of the Covid-19 pandemic, but that access was halted with very little notice. Patients and families members feel strongly that this is unjust and that this treatment should be made available on the NHS for GvHD for all patients in need. The ability to take ruxolitinib at home in pill form is a significant advantage. Patients and carers have a very strong preference for oral 'at home' treatments that allow them to minimise time in hospital, and help to avoid infection risks. One patient Anthony Nolan spoke to was able to access ruxolitinib during the pandemic, having tried several earlier treatments including steroids and ECP without significant impact on their serious acute GvHD. However, with ruxolitinib they felt the positive impact on symptoms was noticeable within a very short space of time. They also noted the ability to take the medication at home, at a time when they were very ill was "*invaluable"* and that ruxolitinib "*ended the cycle of endless treatments".* For this patient it was a "*a life-saving drug".*

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	None.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	This treatment would greatly benefit patients for whom ECP is not suitable due for example to problems with venous access and those who are unable to or would struggle with the time and cost burden of travelling to an ECP centre. Please also see the equality section below. All patients with acute GvHD are in need of new treatment options.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Patients from lower socioeconomic backgrounds and those who live further away from their transplant centre or ECP provider would benefit greatly from new treatment options such as ruxolitinib which they can take at home. In addition, there are international and national inequalities in access to ruxolitinib. Ruxolitinib is the current standard of care for GVHD in many comparable countries, such as North America and countries in Europe. Patients in the UK should be able to access a treatment that is considered standard of care and best practice internationally. Access across the UK itself is also variable, as some patients have been able to access ruxolitinib through the IFR system whilst others cannot. This is highly inequitable. It should also be noted that ruxolitinib was available on an interim basis during the COVID-19 pandemic, therefore there is a cohort of patients started treatment during the pandemic and who are eligible to remain on it, while new patients who fell out of the interim period have not been able to start the treatment. As such, there are inequities of access within individual clinics themselves.

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Acute GvHD is an incredibly difficult condition to live with and can be life threatening. It causes significant negative impacts on the physical and mental health of patients and families. Acute GvHD also has adds to the financial burden faced by post-transplant patients and families. • Current treatments for acute GvHD have significant setbacks. For example, steroids can cause a wide range of side effects and ECP is a time and cost burden on patients and families. • New treatments are urgently needed to ensure more equitable, and convenient ways to manage and treat acute GvHD. • For those whom current acute GvHD treatments are not able to manage their condition, ruxolitinib could be life changing.

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NICE 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 [ID6377]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	British Society of Bone Marrow Transplantation and Cellular Therapy. Also University Hospitals Birmingham
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? **Yes** or No A specialist in the treatment of people with this condition? **Yes** or No A specialist in the clinical evidence base for this condition or technology? **Yes** or No Other (please specify):
5a. Brief description of the organisation	BSBMTCT – is a leading society and data registry for the blood and marrow transplantation and cellular therapy community in the UK. Funded by NHS England and Scotland and also centre membership. UHB – One of the largest trusts in England. BCCTT is one of the largest single units delivering stem cell transplants and cell therapies in England.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No

5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The aim is to elicit a clinical response (complete or partial) as soon as possible in patients. In the steroid refractory setting, acute GvHD carries a very poor prognosis and a transplant related mortality more than 60% within 6-12 months if unresponsive. This importantly includes the ability to titrate off systemic steroids, and reduce the infectious risk faced by this heavily immunocompromised group.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A reduction of organ grading and staging according to the MAGIC / IBMTR consensus scoring of acute GvHD. An ability to decrease systemic steroids. An improvement in patients Quality of Life.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Absolutely yes. England is currently a domestic and international outlier. Ruxolitinib is available in Scotland and Wales creating inequality across Great Britain. We are also an international outlier as Ruxolitinib is considered Standard of Care for this indication in the USA, Canada and in Europe (as evidenced by recent EBMT and Canadian Guidelines – for example). British Guidelines – currently in writing, will also recommend Ruxolitinib in this setting.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	2nd line treatment for steroid refractory acute GvHD in Scotland and Wales is already treated with Ruxolitinib. In England we have a basket of non-licensed agents available, according to the current NHS commissioning document of 2017. This includes ECP, infliximab, alemtuzumab, MMF, sirolimus, ciclosporin. The evidence for these agents are limited to old, non randomised studies with small numbers.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	British Guidelines (currently being updated – will recommend Rux 2nd line), EBMT guidelines 2024 Penack et al, Kim et al Canadian guidelines 2024, both recommend rux 2nd line.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	This has been a difficult time for professionals in England, as Scotland and Wales already have access. Given that the data for the benefit for ruxolitinib comes from the phase 3 RCT REACH 2, it provides us with the best data for supporting its role 2nd line, with significant benefit versus best alternative therapy, and there is a unanimous approach from professionals that this should be available for steroid refractory acute GvHD in England.
9c. What impact would the technology have on the current pathway of care?	Real world data supports the REACH 2 data, and so we could expect a doubling of responses in patients. This would translate to improved survival, but also a reduction in hospitalisation and health care useage. It would also reduce the costs associated with the delivery of ECP in particular. There would also be reduction of costs to patients with swifter recovery and reduced number of attendances for treatment and review.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It would be employed in the same fashion as the temporary commissioning during COVID. Rux 10mg BD.
10a. How does healthcare resource use differ between the technology and current care?	As above I would expect the healthcare resource use to decrease overall with increased rates of response.

10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Tertiary care – transplant unit oversight. This may be in inpatient or outpatient setting. Some patients may present as emergencies to secondary care centres, so whilst they would ideally be initially treated in JACIE accredited transplant units, secondary care centres may have to be able to provide ruxolitinib, and deliver it under the guidance of the parent transplant unit.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	It is a tablet twice a day, so no extra resourcing / tech/ infrastructure is required.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes – as per REACH 2 trial, and real world data.
11a. Do you expect the technology to increase length of life more than current care?	Yes – as per REACH 2 trial.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The general population is probably not the correct comparator group here. The REACH 2 trial looked at all patients with steroid refractory acute GvHD against best alternative therapy and demonstrated a significant benefit against the 'basket' of agents currently available in England.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Easier. Monitoring of blood counts and liver function is important and dose adjustments may be required according to the SmPC. Viral reactivation may occur, but the rates of this were not statistically significantly different between the rux and BAT arms in REACH 2.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	As per previous temporary commissioning during COVID and reach 2, response should be assessed at day 28. Stopping criteria would include – cessation with complete response (following successful cessation and wean of other IST). Progression of GvHD by day 28. Intolerance of ruxolitinib – e g severe cytopenia, liver derangement, infection.
15. Do you consider that the use of the technology will result in any	Yes, Patient reported outcome measures support the benefit of ruxolitinib for patients.

substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes – there is significant improvement likely here for this area which is currently a huge unmet need. The impact on reduction of inequality across Great Britain is also not to be underestimated.
16a. Is the technology a 'step-change' in the management of the condition?	Yes. Targeted treatment.
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes. Otherwise there is no licensed therapy for this condition.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Cytopenias can increase the need for transfusions Liver derangement can lead to difficulties delivering other drugs

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes – BAT arm included the basket of non-licensed medications currently available in England – particularly ECP.
18a. If not, how could the results be extrapolated to the UK setting?	n/a
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Overall response rate d28 and d56. REACH 2. Long term survival
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	n/a
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	no
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no
20. How do data on real-world experience	Comparably.

compare with the trial data?	

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	AS I've stated numerous times in this document England is a domestic and International Outlier with no current commissioned access to ruxolitinib for this indication. This is a significant post code driven inequality for the patients of England.
21b. Consider whether these issues are different from issues with current care and why.	Otherwise there are no inequalities in care – this is a key area of unmet need in England.

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• Ruxolitinib is considered international standard of care for steroid refractory acute GvHD • Pending domestic guideline updates, and internation guidelines verifies this. • Improves overall response rate and overall survival • Current inequality in commissioned access across Great Britain • No other licensed agents available • SR acute GvHD remains a significant contributor to transplant related mortality following allo-SCT.

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NICE 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 [ID6377]

NHS organisation submission (ICBs and NHS England)

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

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- Your response should not be longer than 10 pages.

About you

1. Your name	Fiona Dignan, [redacted]
2. Name of organisation	NHS England Blood and Marrow Transplantation Clinical Reference Group
3. Job title or position	National Specialty Advisor for BMT CRG, [redacted]

4. Are you (please select Yes or No):	Commissioning services for an ICB or NHS England in general? Yes Commissioning services for an ICB or NHS England for the condition for which NICE is considering this technology? Yes Responsible for quality of service delivery in an ICB (for example, medical director, public health director, director of nursing)? No An expert in treating the condition for which NICE is considering this technology? No An expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? Fiona Dignan was an investigator for the REACH 2+3 trials but completing this form in role as NSA for the BMT CRG Other (please specify):
5a. Brief description of the organisation (including who funds it).	The specialised services commissioned by NHS England are grouped into 6 national programmes of care. NHS England Blood and Marrow Transplantation Clinical Reference Group is part of the Blood and Infection Programme of Care.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

Current treatment of the condition in the NHS

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	NHS England Clinical Commissioning Policy https://www.england.nhs.uk/wp-content/uploads/2017/03/gvhd-heamatopoietic-stem-cell.pdf British Society of Blood and Marrow Transplantation and Cellular Therapy – Diagnosis and Management of Acute Graft versus Host Disease https://bsbmtct.org/publication-archive/diagnosis-and-management-of-acute-graft-versus-host-disease/ Consensus recommendations also exist from the European Society for Blood and Marrow Transplantation: 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. Penack O, Marchetti M, Ruutu T, Aljurf M, Bacigalupo A, Bonifazi F, Ciceri F, Cornelissen J, Malladi R, Duarte RF, Giebel S, Greinix H, Holler E, Lawitschka A, Mielke S, Mohty M, Arat M, Nagler A, Passweg J, Schoemans H, Socié G, Solano C, Vrhovac R, Zeiser R, Kröger N, Basak GW.Lancet Haematol. 2020 Feb;7(2):e157-e167. doi: 10.1016/S2352-3026(19)30256-X.

7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway is clearly articulated in the NHSE commissioning policy and the joint BCSH and BSBMTCT guidelines. The commissioning policy includes extracorporeal photopheresis (ECP) as the only treatment for patients who fail first line treatment. The inclusion criteria are included below: Inclusion criteria: (i) Patient presents with continued or relapsed clinical features of aGvHD (maculopapular rash; persistent nausea and/or emesis; abdominal cramps with diarrhoea; and a rising serum bilirubin concentration) as determined by clinical examination OR biopsy where disease constellation is not clear; AND (ii) Is unsuitable for, is steroid-dependent OR shows incomplete response to first-line treatment (combination therapy of topical therapies, calcineurin inhibitors, systemic corticosteroids, sirolimus and/or mycophenolate mofetil). The following interventions are not routinely commissioned for the treatment of acute GVHD: infliximab, etanercept, inolimomab, alemtuzumab, pentostatin or mesenchymal stem cells. In the Joint BCSH and BSBMTCT guidelines other second line treatments are suggested including IL 2 receptor antibodies, anti-TNF antibodies, MTOR inhibitors and mycophenolate mofetil in addition to ECP. Third line options listed include methotrexate, pentostatin, mesenchymal stem cells or alemtuzumab. These other second line treatments are not routinely commissioned in England. There is some variation in practice since some professionals are able to access mesenchymal stem cells or etanercept through individual Trust funding and may use these agents instead of or in addition to ECP.
8. What impact would the technology have on the current pathway of care?	Ruxolitinib would offer an additional second line therapy for patients with steroid refractory acute GvHD. It is an oral therapy and would therefore be easier to deliver than ECP.

The use of the technology

9. To what extent and in which population(s) is the technology being used in your local health economy?	A number of patients commenced ruxolitinib during the Covid-19 pandemic under an NHSE interim Covid-19 commissioning policy, in order to reduce the need for immunocompromised people to travel for access to ECP therapy on a regular basis. The interim policy concluded in March 2022; those who started on ruxolitinib were able to continue treatment. Audit data from 1st November 2020 to 31st December 2021 showed that 48 patients received ruxolitinib for acute GVHD ([redacted], personal communication, BMT CRG ruxolitinib audit)
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Ruxolitinib is not currently routinely commissioned for the treatment of acute GVHD for new patients. This technology is likely to be used as per the previous NHSE interim Covid-19 commissioning policy which concluded in March 2022 as described above.
10a. How does healthcare resource use differ between the technology and current care?	There is a significant difference in healthcare resource between the proposed technology and current standard of care. The current treatment pathway includes ECP as a second line treatment. This is resource intensive since it requires the appropriate apheresis equipment, physical space and appropriately trained staff. Patients must attend for ECP treatment twice a week and usually require several months of therapy. The treatment takes several hours to deliver and often requires patients to receive blood transfusions or platelet transfusions ahead of therapy so that they can undergo the apheresis treatment safely. This requirement can mean extra pressure on transfusion laboratories and patients spending extra time on haematology day units while they receive the transfusions. The ECP treatment also requires adequate venous access. In many patients, this means that an indwelling catheter (tesio line) is required. These lines are usually inserted by the interventional radiology department and there is often pressure on available slots. Indwelling venous catheters frequently develop infections or blood clots which can lead to patients requiring in-patient hospital admission for antibiotics or patients requiring anti-coagulation therapy. The indwelling lines have to be cared for regularly and so patients may have to attend for extra visits for line care or receive this care from district nursing teams in the community.

	The presence of an indwelling line can also adversely affect patients' quality of life and mental health. It is often viewed as a "step backwards" as they have had an indwelling line earlier during their transplant admission. In addition, it can restrict their activities as the line site needs to be kept dry to prevent the risk of infection. The proposed technology is an oral therapy that patients can take at home.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This technology will be used in specialist clinics in secondary and tertiary care. The majority of patients would have the treatment prescribed by the specialist stem cell transplant unit. Patients would either take the medication at home or receive it as part of their in-patient medication if their symptoms were bad enough to necessitate hospital admission.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None
10d. If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	Ruxolitinib therapy would not require any additional testing. Patients would be monitored for infections and also have their full blood counts, liver and renal function monitored but this would be standard of care following a transplant. Ruxolitinib would be stopped if patients developed side effects as a consequence of the drug including significant cytopenias or infectious complications. It would also be stopped if there was no complete or partial response observed in the patient's acute GVHD symptoms.
11. What is the outcome of any evaluations or audits of the use of the technology?	A randomised controlled trial supports the use of ruxolitinib in this setting. Zeiser et al reported on a phase 3, randomised, open-label study (REACH 2) in patients aged 12 and over. 309 patients underwent randomisation between ruxolitinib and investigator's choice of therapy (control group) The primary end point was overall response (complete or partial response) at day 28. The trial showed that overall response was higher in the ruxolitinib group than in the control group (62% versus 39%, $P < 0.001$). The secondary end point was durable overall response at day 56. The trial showed that the overall response at day 56 was higher in the ruxolitinib group than the control group (40% versus 22%, $P < 0.001$).

	These results were reflected in a UK audit that was undertaken of the use of ruxolitinib during the Covid-19 pandemic. Forty-eight patients received ruxolitinib for acute GVHD. 37 patients had a complete or partial response to therapy at day 28 and 24 had a complete or partial response by day 56 (Nick Duncan, personal communication, BMT CRG ruxolitinib data)

Equality

12a. Are there any potential equality issues that should be taken into account when considering this treatment?	This technology will reduce health inequalities because it will offer an alternative treatment option to ECP. This would benefit individuals who have difficulties and challenges with travelling to receive ECP either due to work or caring commitments, disability or other reasons. As described above, patients must travel to a specialist centre to receive ECP on a regular basis. Some patients live a long distance away from the centre and rely on patient transport services which mean that they can be reluctant to receive the treatment as it can often mean spending two full days away from home. The new technology (ruxolitinib) is an oral tablet which patients can take at home. The new technology is also available to patients who live in Scotland as it has previously been approved for use there so introducing it as a treatment in England would help to reduce this inequality
12b. Consider whether these issues are different from issues with current care and why.	As described above, the new technology would help to reduce inequalities.

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

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 6 September 2024

Source of funding: This report was commissioned by the National Institute for Health Research (NIHR) Evidence Synthesis Programme as project number 168130.

Declared competing interests of the authors: None.

Acknowledgements: We gratefully acknowledge the expert clinical advice input from Dr Andrew Gennery, Professor/Honorary Consultant in Paediatric Immunology and HSCT, Institute of Translational and Clinical Research, and Dr Francesca Kinsella, Consultant Haematologist, Director of the Birmingham Centre for Cellular Therapy and Transplantation, Honorary Senior Lecturer Institute of Immunology and Immunotherapy, Birmingham ECMC Immunotherapy Lead.

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This report should be referenced as follows:

Armstrong N, Corro Ramos I, Qendri V, van Dongen-Leunis A, Patel M, Tian X, Chen J, Stirk L, Al M, and Wolff R. Ruxolitinib for treating acute graft-versus-host- disease refractory to corticosteroids in people aged 12 and over [ID6377]: a Single Technology Assessment. York: Kleijnen Systematic Reviews Ltd, 2024.

Contributions of authors:

Nigel Armstrong acted as project lead, health economist and systematic reviewer on this assessment, critiqued the company's economic evaluation and the clinical effectiveness methods and evidence and contributed to the writing of the report. Isaac Corro Ramos acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Venetia Qendri, Annemieke van Dongen-Leunis, and Xiaoyu Tian acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Mubarak Patel, Xiaoyu Tian and Jiongyu Chen acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Lisa Stirk critiqued the search methods in the submission and contributed to the writing of the report. Maiwenn Al acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance. Robert Wolff critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

AdViSHE	Assessment of the Validation Status of Health-Economic decision models
AE	Adverse events
AFT	Accelerated Failure Time
aGvHD	Acute graft-versus-host disease
AIC	Akaike Information Criterion
alloSCT	Allogenic stem cell transplant
ALT	Alanine aminotransferase
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
ASH	American Society of Haematology
ASTCT	American Society for Transplantation and Cellular Therapy
ATC	Anatomical therapeutic chemical
ATG	Anti-thymocyte globulin
BAT	Best available therapy
BEL	Belumosudil
BIC	Bayesian Information Criterion
BID	Twice daily
BNF	British National Formulary
BOPA	British Oncology Pharmacy Association
BOR	Best overall response
BSA	Body surface area
[redacted]	
CADTH	Canadian Agency for Drugs and Technologies in Health
CE	Cost effectiveness
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
cGvHD	Chronic graft-versus-host disease
CI	Confidence interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CMV	Cytomegalovirus
CNI	Calcineurin inhibitor
CON	Confidential
cPAS	Comparator Patient Access Scheme
CR	Complete response
CS	Company submission
CSR	Clinical Study Report
DLI	Donor lymphocyte infusion
DOR	Duration of response
DP	Decision problem
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EAG	Evidence Assessment Group
EBMT	European Bone Marrow Transplant
ECM	Established Clinical Management
ECP	Extracorporeal photopheresis
EFS	Event-free survival
EHA	European Hematology Association
eMIT	Electronic market information tool
EQ-5D(-5L)	European Quality of Life-5 Dimensions-5 Levels
EQ-5D-3L	European Quality of Life-5 Dimensions-3 Levels
EOS	End of study
EOT	End of treatment

ESHPM	Erasmus School of Health Policy & Management
EUR	Erasmus University Rotterdam
FAD	Final Appraisal Document
FAS	Full analysis set
FDA	Food and Drug Administration
FF	Failure-free
FFS	Failure-free survival
G-BA	Gemeinsamer Bundesausschuss
GvHD	Graft-versus-host disease
HAS	Haute Autorité de Santé
HCRU	Health care resource utilisation
HLA	Human leukocyte antigen
HR	Hazard ratio
HRQoL	Health-related quality of life
HSE	Health Survey for England
HSUV	Health state utility value
HTA	Health Technology Assessment
ICF	Informed consent form
ICER	Incremental cost-effectiveness ratio
ICER	Institute for Clinical and Economic Review
iDBC	Disease burden calculator
IMR	Incidence of malignancy relapse
iMTA	Institute for Medical Technology Assessment
Inc.	Incremental
IQWiG	German Institute for Quality and Efficiency in Health Care
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IV	Intravenous
JK	Janus kinase
KM	Kaplan-Meier
KSR	Kleijnen Systematic Reviews Ltd
LYG	Life years gained
MAGIC	Mount Sinai acute GvHD International Consortium
MedRA	Medical Dictionary for Regulatory Activities
MMF	Mycophenolate mofetil
MRU	Medical resource use
MSC	Mesenchymal stromal cells
MSM	Multi-state model
mTOR	Mammalian target of rapamycin
MTX	Methotrexate
N/A	Not applicable
NCPE	National Centre for Pharmacoeconomics
NE	Not estimated
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NL	The Netherlands
NMA	Network meta-analysis
NR	Not reported
NRM	Non-relapse mortality
NSAID	Non-steroidal anti-inflammatory drug
NST	New systemic therapy
ORR	Overall response rate
OS	Overall survival
PAS	Patient Access Scheme

PBAC	Pharmaceutical Benefits Advisory Committee
PBSC	Peripheral blood stem cell
PD	Progressive disease
PH	Proportional hazard
PK	Pharmacokinetics
PR	Partial response
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PT	Preferred term
QALY	Quality-adjusted life year
QD	Once daily
QoL	Quality of life
RCT	Randomised controlled trial
RE	Random effects
RePeC	Research Papers in Economics
SAE	Serious adverse event
SBU	Swedish Agency for Health Technology Assessment and Assessment of Social Services
SD	Standard deviation
SD	Stable disease
SE	Standard error
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SOC	System organ class
SR-aGvHD	Steroid-refractory acute graft-versus-host disease
TA	Technology Appraisal
TAS	Therapeutic apheresis services
TKI	Tyrosine kinase inhibitor
TSD	Technical Support Document
TTR	Time to response
Tx	Treatment
UK	United Kingdom
USA	United States of America
VBA	Visual Basic for Applications
VGPR	Very good partial response
WBC	White blood cell
WHO	World Health Organization
WTP	Willingness-to-pay

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1. Executive summary

This summary provides a brief overview of the key issues identified by the Evidence Assessment Group (EAG) as being potentially important for decision making. If possible, it also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 presents the key model outcomes. Section 1.3 discusses the decision problem, Section 1.4 issues related to the clinical effectiveness, and Section 1.5 issues related to the cost effectiveness. A summary in presented in Section 1.6.

Background information on the condition, technology and evidence and information on key as well as non-key issues are in the main EAG report, see Sections 2 (decision problem), 3 (clinical effectiveness) and 4 (cost effectiveness) for more details.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1.1: Summary of key issues

ID1457	Summary of issue	Report Sections
1	A single comparator of BAT, which is a mixture of ECP and other therapies, might overlook distinct subgroups or overestimate the treatment effect in UK clinical practice.	2.1, 2.2, 2.5, 3.2, and 4
2	Clinical effectiveness evidence lacking in applicability to adolescents and Grade I disease.	2.1, 3.2, and 4
3	Potential underestimate of the treatment effect on cGvHD incidence.	3.2
4	REACH1 has worse outcomes for ruxolitinib than in REACH2, which is the key trial.	3.2
5	The likely mixture of patients (in terms of treatment response and/or resolution of symptoms) in the failure-free health states is not completely captured in the model.	4.2.2
6	Lack of alignment between the chronic population in the model and the population in REACH3.	4.2.3
7	The EAG does not agree (in general) with the choices made by the company to extrapolate (FF) survival data.	4.2.6
8	Uncertainty about the implementation of health state utilities (some of the health state utility values and some modelling assumptions).	4.2.8

BAT = best available therapy; cGvHD = chronic graft-versus-host disease; EAG = Evidence Assessment Group; ECP = extracorporeal photopheresis; FF = failure-free; UK = United Kingdom

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are the following:

- Adopting a multiplicative approach to calculating adverse event disutilities.
- Assuming a benefit for ruxolitinib versus BAT for time to new systemic therapy (NST) only.
- Using utility values for chronic graft-versus-host disease (cGvHD) health states in the first four model cycles equal to the utility values in the acute graft-versus-host disease (aGvHD) health

states (the latter are lower – to account for patients transitioning to the chronic health state without resolution of acute symptoms).

1.2 Overview of key model outcomes

NICE Technology Appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing overall survival (OS) (higher number of life years).
- Increasing the number of QALYs in failure-free (aGvHD) and in cGvHD.
- Slightly decreasing the number of QALYs in NST (aGvHD).

Overall, the technology is modelled to affect costs by:

- Its lower acquisition and subsequent treatment costs compared to best available therapy (BAT).
- Increasing disease management and cGvHD treatment costs.
- A minor increase in costs due to adverse events (AEs).

The modelling assumptions that have the greatest effect on the ICER are:

- Changes in BAT costs.
- Scenarios where different graft-versus-host disease (GvHD) resource use/costs were not included resulted in very low ICERs.
- The highest ICER was £30,022 (£25,018 with severity weighting), when for all transitions from failure-free (FF) joined models were assumed, with the choice of the parametric shape based on clinical input.

1.3 The decision problem: summary of the EAG's key issues

Table 1.2: Key issue 1: A single comparator of BAT, which is a mixture of ECP and other therapies, might overlook distinct subgroups or overestimate the treatment effect in UK clinical practice

Report Sections	**2.1, 2.2, 2.5, 3.2, and 4**
Description of issue and why the EAG has identified it as important	There appear to be at least two subgroups each with a different comparator treatment, one being ECP, where patients have to be haematologically stable and have good venous access. This would imply a subgroup where patients are not haematologically stable and/or do not have good venous access. This contrasts with the approach of a using a comparator that is mixture of ECP and other treatments, referred to as BAT, which might lead to a bias in relative effectiveness and cost effectiveness if the percentage of patients receiving ECP in UK clinical practice is higher than that in the REACH2 trial or the cost effectiveness analysis. Indeed, both EAG clinical experts reported that ECP should be offered to most patients.
What alternative approach has the EAG suggested?	Subgroup analysis by patients eligible or not eligible for ECP.
What is the expected effect on the cost effectiveness estimates?	The ICER for the ECP eligible subgroup is likely to go up, although difficult to predict due to crossover in the trial and change in cost.

Report Sections	2.1, 2.2, 2.5, 3.2, and 4
What additional evidence or analyses might help to resolve this key issue?	Comparison between ruxolitinib and individual BAT treatments, at least ECP by itself. A systematic review comparing various forms of ECM including ECP and any comparator treatments. Cost effectiveness analyses including all relevant comparators would also be required.
BAT = best available therapy; EAG = Evidence Assessment Group; ECM = Established Clinical Management; ECP = extracorporeal photopheresis; ICER = incremental cost-effectiveness ratio; UK = United Kingdom	

Table 1.3: Key issue 2: Clinical effectiveness evidence lacking in applicability to adolescents and Grade I disease

Report Sections	2.1, 2.2, 2.5, 3.2, and 4
Description of issue and why the EAG has identified it as important	The scope and decision problem (DP) are for people aged 12 years and over, and without limiting by grade of disease. However, the eligibility criteria for the REACH trials preclude Grade I disease. Also, the baseline characteristics of the REACH trials reveal that there were no patients in REACH1 and only about 3% in REACH2 who are adolescents (under age 18).
What alternative approach has the EAG suggested?	Provide a justification for the inclusion of adolescents and Grade I disease or exclude from the DP.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Further evidence to support the effectiveness and cost effectiveness in these subgroups.
DP = decision problem; EAG = Evidence Assessment Group	

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Table 1.4: Key issue 3: Potential underestimate of the treatment effect on cGvHD incidence

Report Section	3.2
Description of issue and why the EAG has identified it as important	The treatment effect on cGvHD favoured BAT. However, given that death would preclude progression to cGvHD and that crossover appears to increase OS, it seems likely that crossover also inflated the incidence of cGvHD, which means that ruxolitinib might have a worse effect in comparison to ECM in clinical practice than observed in the trial. This is, of course, made more uncertain by any mismatch between BAT and ECM. The company used the same incidences for ruxolitinib and BAT in their clarification response, which does not satisfactorily address this issue.
What alternative approach has the EAG suggested?	None.
What is the expected effect on the cost effectiveness estimates?	Unknown.

Report Section	3.2
What additional evidence or analyses might help to resolve this key issue?	Adjustment for crossover applied to BAT and ideally also applied to ECP (see Key issue 1).
BAT = best available therapy; cGvHD = chronic graft-versus-host disease; EAG = Evidence Assessment Group; ECM = Established Clinical Management	

Table 1.5: Key issue 4: REACH1 has worse outcomes for ruxolitinib than in REACH2, which is the key trial

Report Section	3.2
Description of issue and why the EAG has identified it as important	Although REACH2 is the key trial, being an RCT, REACH1 did show poorer survival outcomes: for median FFS, 2.80 months vs 4.86 months and, for median OS, 7.63 vs 10.71 months. There is no clear explanation for this.
What alternative approach has the EAG suggested?	None.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Provide some explanation for the difference between REACH2 and REACH1.
EAG = Evidence Assessment Group; FFS = failure-free survival; OS = overall survival; RCT = randomised controlled trial	

1.5 The cost effectiveness evidence: summary of the EAG's key issues

A full summary of the cost effectiveness (CE) evidence review conclusions can be found in Section 6.4 of this report. The company's CE results are presented in Section 5, the EAG's summary and detailed critique are in Section 4, and the EAG's amendments to the company's model and results are presented in Section 6. The key issues in the CE evidence are discussed in Tables 1.6 to 1.9.

Table 1.6: Key issue 5: The likely mixture of patients (in terms of treatment response and/or resolution of symptoms) in the failure-free health states is not completely captured in the model

Report Section	4.2.2
Description of issue and why the EAG has identified it as important	Response to treatment is not implicitly included in the model and it seems that the FF health state includes a mixture of patients who are still experiencing aGvHD symptoms and those that are in remission after treatment response. It seems likely that this mixture changes over time, as those who continue to experience aGvHD symptoms will probably transition to another treatment (NST). This might explain why the utilities observed in REACH2 increase during the first 20 weeks (see Table 4.7 in Section 4.2.8). This might be interpreted as an attempt to account for those patients achieving remission after treatment response, but it is uncertain. This distinction is expected to be relevant for patients who transition from FF aGvHD to another health state. For example, patients in FF transitioning to cGvHD (FF) for whom their aGvHD symptoms are not yet resolved would presumably have worse survival and QoL

Report Section	4.2.2
	outcomes than those in FF in remission after treatment response transitioning to cGvHD.
What alternative approach has the EAG suggested?	Using alternative transition probabilities, utilities and costs conditional on symptoms resolution.
What is the expected effect on the CE estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	Collecting data on different subgroups allowing estimation of input parameters by symptom resolution.
aGvHD = acute graft-versus-host disease; cGvHD = chronic graft-versus-host disease; CE = cost effectiveness; EAG = Evidence Assessment Group; FF = failure-free; NST = new systemic therapy; QoL = quality of life	

Table 1.7: Key issue 6: Lack of alignment between the chronic population in the model and the population in REACH3

Report Section	4.2.3
Description of issue and why the EAG has identified it as important	The EAG considers that there seems to be a mismatch between the chronic population intended to be modelled and the population in REACH3: in REACH3 only 10.4% of patients had SR-aGvHD, whereas the model assumes 100%. It is also unclear whether for these patients in REACH3 the symptoms of aGvHD were resolved or not.
What alternative approach has the EAG suggested?	Using alternative transition probabilities (and possibly utilities and costs) for the modelled chronic population.
What is the expected effect on the CE estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	Evidence supporting the alignment of the chronic population in the model and in REACH3. If necessary, re-estimation of all model parameters for the chronic population.
aGvHD = acute graft-versus-host disease; CE = cost effectiveness; EAG = Evidence Assessment Group; SR-aGvHD = steroid-refractory- acute graft-versus-host disease	

Table 1.8: Key issue 7: The EAG does not agree (in general) with the choices made by the company to extrapolate (FF) survival data

Report Section	4.2.6
Description of issue and why the EAG has identified it as important	The company's approach to survival data extrapolation seems to lack consistency, which in some cases results in implausible and/or contradictory decisions.
What alternative approach has the EAG suggested?	Adopting a pragmatic approach where the only benefit of ruxolitinib over BAT would be on delaying time to NST. For the other transitions, acknowledging the outstanding uncertainties, these could be considered equal between both arms.
What is the expected effect on the CE estimates?	Unclear.

Report Section	4.2.6
What additional evidence or analyses might help to resolve this key issue?	Reassessing the survival analysis in a consistent and systematic way, avoiding implausible and/or contradictory decisions. Using alternative fitted parametric models for time to events (used to derive transition probabilities)
BAT = best available therapy; CE = cost effectiveness; EAG = Evidence Assessment Group; FFS = failure-free survival; NST = new systemic therapy	

Table 1.9: Key issue 8: Uncertainty about the implementation of health state utilities (some of the health state utility values and some modelling assumptions)

Report Section	4.2.8
Description of issue and why the EAG has identified it as important	The EAG is concerned about the appropriateness of pooling the data from REACH2 and REACH3 to fit a single statistical model to estimate health state utility values because these trials include different patient and disease populations (see also Key issue 6). The choice of the preferred model seems to be based upon clinical expert opinion only. The estimated utility values for some health states might lack face validity. Special attention is required for patients with chronic disease for whom acute symptoms are not resolved.
What alternative approach has the EAG suggested?	Alternative fitted regression models for utilities using separate statistical models for the utility values for aGvHD (REACH2) and cGvHD (REACH3). The company did not provide the variance-covariance matrices for these separate models, therefore, the EAG is unable to include these in an EAG preferred base-case. The choice of the preferred model could also be guided by goodness-of-fit statistics. Re-assess the validity of the estimated utility values (clinical experts, literature, etc.).
What is the expected effect on the CE estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	Evidence supporting the alignment of the chronic population in the model and in REACH3, such as a comparison of utilities of REACH2 patients who developed cGvHD and utilities of REACH3 patients who had SR-aGvHD. Reassessing of the regression analyses and validate the estimated values.
aGvHD = acute graft-versus-host disease; cGvHD = chronic graft-versus-host disease; CE = cost effectiveness; EAG = Evidence Assessment Group	

1.6 Summary of the EAG's view

The step-by-step changes made by the EAG to derive its base-case, using the company submission (CS) base-case and the model submitted after clarification as starting point, can be seen in Table 1.10. The change with the largest impact on the results was the assumption that time from failure-free to relapse and to death would be the same for both treatments. This change led to a substantially lower ICER; though the incremental QALYs decrease as patients in BAT live slightly longer and in ruxolitinib slightly shorter, the incremental costs also decrease. Correcting the indexed cost of rehospitalisation

increases the incremental costs and ICER slightly, whilst the impact of the other changes made by the EAG was negligible.

Table 1.10: Individual impact of EAG preferred assumptions

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	ICER severity weighted (£/QALY)
CS base-case						
BAT	79,632	1.37	–			
Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	33,133	27,611
CS base-case after the clarification						
BAT	79,292	1.32	–			
Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	30,193	25,161
Correction of errors on sheet 'Survival data' (1)						
BAT	79,292	1.32				
Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	26,235	21,862
(1) + Correction error indexing cost rehospitalisation						
BAT	80,521	1.32	-	-		
Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	27,243	22,703
(1) + Ruxolitinib only different time to NST						
BAT	82,580	1.39	-	-		
Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	19,960	16,633
(1) + Utility cGvHD ≤ 4 cycles equal to failure-free <= 4 cycles						
BAT	79,292	1.31	-	-		
Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	26,229	21,858
(1) + Disutility AE multiplicative						
BAT	79,292	1.32	-	-		
Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	26,214	21,845
All changes combined (EAG base-case)						
BAT	83,878	1.39	-	-		
Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	20,987	17,489

Based on updated economic model, following the clarification phase[1]

AE = adverse event; BAT = best available therapy; cGvHD = chronic graft-versus-host disease; CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; NST = new systemic therapy; QALY = quality-adjusted life year

2. Critique of company's definition of decision problem

Table 2.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG comment
Population	People aged 12 years and older with aGvHD who have inadequate response to corticosteroids	As per final scope	In line with final scope	The EAG have identified a potential lack of evidence for adolescents and Grade I disease given the exclusion of the latter and lack of patients in the former categories in the REACH trials. The EAG identified that there appeared to be at least two subgroups each with a different comparator treatment, one being ECP, where patients have to be haematologically stable and have good venous access. This would imply a subgroup where patients are not haematologically stable and/or do not have good venous access. However, EAG clinical expert opinion would suggest that most patients would be eligible for ECP.
Intervention	Ruxolitinib	As per final scope	In line with final scope	Not an issue
Comparator(s)	ECM without ruxolitinib, including but not limited to: ECP Combination therapy with mammalian target of rapamycin inhibitors (for example, sirolimus) and/or mycophenolate mofetil	As per final scope	In line with final scope	According to the potential subgroups, it appears that ECP is applicable for one and off label therapies such as etanercept, infliximab, mesenchymal stromal cells (MSC), and sirolimus, for those not suitable for ECP

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG comment
Outcomes	The outcome measures to be considered include: Response to treatment (including CR and OR) Mortality (including non-relapse mortality) FF survival Adverse effects of treatment HRQoL	As per final scope	In line with final scope	The EAG identified a potential issue with the definition of FF survival
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective The availability of any commercial arrangements for the intervention, comparator and subsequent	Not completed	Not completed	As per the reference case

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG comment
	treatment technologies will be taken into account			
Special considerations including issues related to equity or equality	N/A	ECP availability is limited to five TAS units in England, and a limited number of hospital trusts providing ECP services independently. This means patients with aGvHD must travel to receive treatment, thereby increasing their risk of infections. Furthermore, eligibility for ECP also depends on patients having good venous access and being haematologically stable, therefore not all patients are able to receive this treatment option. Some centres in England will use their own budgets to enable patient access to ruxolitinib. Additionally, some patients self-fund or use private healthcare. This creates inequity of access to ruxolitinib in patients with GvHD across England. In Wales and Scotland, patients have access to ruxolitinib, which creates inequity of access across the UK.	Issues related to ECP and ruxolitinib access were raised by UK clinical experts consulted as part of this submission.	See the Population Section above. In addition, it might be that the appropriate comparator for those patients who do not have access to ECP is one of the other treatments or combinations, although this might lead to an inefficient allocation or resources if ECP would be cost effective versus those other treatments

Based on Table 1 and pages 10 to 12 of the CS[3]

aGvHD = acute graft-versus-host disease; CR = complete response; CS = company submission; EAG = Evidence Assessment Group; ECP = extracorporeal photopheresis; ECM = Established Clinical Management; FF = failure-free; GvHD = graft-versus-host disease HRQoL = health-related quality of life; MSC = mesenchymal stromal cells N/A = not applicable; NHS = National Health Service; NICE = National Institute of Health and Care Excellence; OR = overall response; PSS = Personal Social Services; QALY = quality-adjusted life year; TAS = therapeutic apheresis services; UK = United Kingdom

2.1 Population

The population defined in the scope is:[2] people aged 12 years and older with acute graft-versus-host disease (aGvHD) who have inadequate response to corticosteroids, which is the population in the decision problem (DP),[3] and in the UK marketing authorisation.[4]

EAG comment: The scope and DP are for people aged 12 years and over, and without limiting by grade of disease. However, the eligibility criteria for the REACH trials preclude Grade I disease. Also, the baseline characteristics of the REACH trials reveal that there were no patients in REACH1 and only about 3% in REACH2 who are adolescents (under age 18). The EAG therefore requested the company to provide a justification for the inclusion of adolescents and Grade I disease or exclude from the DP, to which they responded that they wanted to retain adolescents and Grade I disease in the DP.[5] They argued that, *"In line with clinical expert opinion…",*(p. 3) the manifestation of the disease, pathophysiology and standard treatments do not differ between adolescents and adults. No justification for assuming similar treatment effect was provided for Grade I disease. Given the lack of evidence of similarity of treatment effect for both adolescents and Grade I disease, the EAG consider that this remains a key issue.

The company submission (CS) states that, based on feedback from United Kingdom (UK) clinical experts, *"If ECP is not an option, UK clinical experts will use off-label therapies such as etanercept, infliximab, mesenchymal stromal cells (MSC), and sirolimus."* (p. 26)[3] This implies that if extracorporeal photopheresis (ECP) is an option then that would be the treatment of choice. The criteria that are listed for ECP to be an option are that a patient is haematologically stable, has good venous access, and has access to a site that offers this treatment. Therefore, the EAG asked the following Clarification Questions:[6]

1. Please clarify if this means that there are effectively two subgroups, one with patients who are haematologically stable with good venous access, and the other who are either not haematologically stable or have poor venous access?
2. Please provide an estimate of the percentage of the total aGvHD population who would be in each of these subgroups.
3. Please clarify that for those who are haematologically stable and have good venous access, the only reason to not administer ECP and instead prescribe another treatment is lack of access to a site that offers ECP. What percentage of patients do not have access to ECP?
4. Please provide clinical effectiveness and cost effectiveness analyses (CEA) for two separate comparisons:
    a. Between ruxolitinib and ECP, on the assumption that these results would be applicable those who are haematologically stable and have good venous access.
    b. Between ruxolitinib and a comparator formed by all other types of Established Clinical Management (ECM), on the assumption that these results would be applicable to those who are not haematologically stable or have poor venous access.

The company responded that there are factors beyond haematological stability and venous access that determine treatment choice.[5] They refused to conduct a subgroup analysis because of this and because clinical experts stated that it was not appropriate, that there were no data for such an analysis and that randomisation would be broken by separate comparisons. The EAG consider that, even if there are other clinical criteria that are used to determine choice of treatment, these do imply different sets of patients who could potentially be identified in clinical practice. These therefore constitute different subgroups,

each with a different comparator, one of which would be ECP. On the other hand, the EAG also agree that such an analysis using the REACH2 data could introduce bias given that patients will have been selected for comparator treatment, although it might be that those criteria would have no effect on prognosis with ruxolitinib. There is also a bias in favour of the comparator due to crossover (see Section 3.2). The problem would also be mitigated if the percentage of patients receiving each of the ECM treatments in REACH2 was the same as in UK clinical practice, but this is not the case for example for ECP, 27% in the trial versus 46% according to clinical expert opinion (Table 20, CS).[3] It is also unclear why so few patients received ECP in the trial especially given that the clinical expert figure seems low in comparison to the opinion expressed by both of the EAG clinical experts that most patients would be considered for ECP (see Appendix 1).[7] One clinical expert is a paediatrician, but the company have argued that there is no difference between adolescents and adults in ECM. Therefore, it might be that not only subgroup analysis according to treatment eligibility is relevant, but that in fact most patients would be eligible for ECP. If this is the case, then it might be that selection bias is less of a problem in a comparison between ECP and ruxolitinib using REACH2. The EAG have shown an analysis of failure-free survival (FFS) by each best available therapy (BAT), as presented in the cost effectiveness Section of the CS and referred to in the clarification latter response, which included an analysis of overall survival (OS) (see Section 3.2). This appears to show that ECP was at least one of the most effective three treatments, although no summary statistics were reported. However, a publication was found that stated that ECP was the best BAT therapy for FFS, the data unfortunately being unpublished.[8] In conclusion, even if evidence to resolve this problem is difficult to find, this continues to be a key issue and the EAG would still recommend the presentation of outcome data for each of the treatments in REACH2, at least for ECP. A systematic review would also be useful as supporting evidence as to the relative effectiveness of ECP versus other ECM treatments.

2.2 Intervention

The intervention in the scope matches that in the DP, which is ruxolitinib.[2, 3]

EAG comment: There might potentially be a mismatch between the intervention dose and concomitant treatments between the REACH trials and UK clinical practice. However, the nature and size of this cannot be determined until the administration of the intervention in clinical practice.

2.3 Comparators

The CS[3] states that the comparators are those of the National Institute for Health and Care Excellence (NICE) scope, that is: established clinical management without ruxolitinib, including but not limited to:

- extracorporeal photopheresis
- combination therapy with mammalian target of rapamycin inhibitors (for example, sirolimus) and/or mycophenolate mofetil.

However, in the CEA, a single comparator was employed, which is referred to as best available therapy (BAT), as in REACH2.[3]

EAG comment: As stated in Section 2.1, it appears that the choice between ECP and the other treatments is driven by clinical characteristics i.e., haematological stability and venous access. This implies that subgroup analysis should be used with the comparator varying by subgroup, with one being ECP. The use of BAT as comparator is liable to lead to a bias in the effectiveness of ruxolitinib versus

BAT and cost effectiveness analysis if the proportion of patients who currently receive ECP in UK clinical practice is different to that in REACH2 (27%) or assumed in the economic model (45%).[3] Of course, it should be noted that crossover in REACH2 (see Section 3.2) is liable to reduce this bias, although the extent of this is uncertain. However, as discussed at length in Section 2.1, given the likely much higher rate of use of ECP in UK clinical practice and some evidence that ECP was probably the most effective of the BAT therapies, the EAG continues to recommend the presentation of an analysis of ruxolitinib versus ECP alone from the REACH2 trial.

2.4 Outcomes

The outcomes in the DP include those in the scope i.e:[2, 3]

- response to treatment (including complete response [CR] and overall response [OR])
- mortality (including non-relapse mortality)
- failure-free (FF) survival
- adverse effects of treatment
- health-related quality of life (HRQoL).

EAG comment: The company were asked to provide some clarification on FF survival in the REACH trials, which is addressed in more detail in Section 3.3.[6]

2.5 Other relevant factors

The company noted that some patients might not have access to ECP.[3]

EAG comment: This might imply that the appropriate comparator for these patients cannot be ECP, even if they are eligible for that treatment. However, this could lead to an inefficient allocation of resources if ECP would be cost effective versus those treatments that the patients with no access to it currently get.

3. Clinical effectiveness

3.1 Critique of the methods of review(s)

3.1.1 Searches

The following paragraphs contain summaries and critiques of the searches related to clinical effectiveness presented in the CS.[3] The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence-based checklist for the Peer Review of Electronic Search Strategies (PRESS) was used to inform this critique.[9] The EAG has presented only the major limitations of each search strategy in the report.

Appendix D of the CS details the systematic literature review (SLR) conducted to identify relevant clinical evidence on the efficacy and safety of ruxolitinib and relevant comparators for the treatment of patients with steroid-refractory aGvHD or chronic graft-versus-host disease (cGvHD) aged ≥12 years.[10] The searches were conducted in November 2019, with updates in September 2021 and January 2024.

A summary of the sources searched is provided in Table 3.1.

Table 3.1: Data sources for the clinical effectiveness systematic review (as reported in CS)

Resource	Host/Source	Date Ranges	Date searched
Electronic databases			
Embase	Ovid	1974-15.11.19 Nov 2019-9.9.21 10.9.21-10.1.24	15.11.19 10.9.21 11.1.24
MEDLINE (inc. In Process & Other Non-Indexed Citations and Daily)	Ovid	1946-15.11.19 Nov 2019-9.9.21 10.9.21-10.1.24	15.11.19 10.9.21 11.1.24
CENTRAL	Ovid	Inception-Oct 2019 Nov 2019-Aug 2021 2021-Dec 2023	15.11.19 10.9.21 11.1.24
Conferences			
• ASH annual conference • EHA annual meeting • EBMT annual meeting • Tandem meetings: ASTCT/CIBMRT • BOPA • ISPOR • ISPOR Europe	Internet	2021-2023 2021-2023 2021-2023 2021-2024 2021-2023 2021-2023 2021-2023	Mar 2024
HTA Agencies			
• NICE • NCPE • SMC • HAS • IQWiG	Internet	No date limit	Feb 2024

Resource	Host/Source	Date Ranges	Date searched
• G-BA • SBU • CADTH • PBAC • ICER			
Trials registries			
• ClinicalTrials.gov • WHO ICTRP	Internet		11.3.24

ASH = American Society of Haematology; ASTCT = Transplantation & Cellular Therapy Meetings of the American Society for Transplantation and Cellular Therapy; BOPA = British Oncology Pharmacy Association; CADTH = Canadian Agency for Drugs and Technologies in Health; CENTRAL = Cochrane Central Register of Controlled Trials; CIBMTR = Center for International Blood and Marrow Transplant Research; CS = company submission; EBMT = European Bone Marrow Transplant; EHA = European Hematology Association; G-BA = Gemeinsamer Bundesausschuss; HAS = Haute Autorité de Santé; ICER = Institute for Clinical and Economic Review; IQWiG = German Institute for Quality and Efficiency in Health Care; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; NCPE = National Centre for Pharmacoeconomics; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; SBU = Swedish Agency for Health Technology Assessment and Assessment of Social Services; SMC = Scottish Medicines Consortium; WHO ICTRP = World Health Organization International Clinical Trials Registry Platform

EAG comment:

- Searches were undertaken in November 2019, with updates in September 2021 and January 2024 to identify clinical evidence on the efficacy and safety of ruxolitinib and relevant comparators for the treatment of patients with steroid-refractory aGvHD or cGvHD aged ≥12 years. The CS, Appendix D and the company's response to clarification provided sufficient details for the EAG to appraise the literature searches.[3, 5, 10]
- A wide range of bibliographic databases, conferences, Health Technology Assessment (HTA) agency websites and trials registries were searched. Reference checking was conducted.
- Searches were extremely well structured, transparent and reproducible, and made good use of free text, subject indexing terms and the available database syntax.
- The database searches for the clinical effectiveness SLR combined facets for graft-versus-host disease (GvHD) and steroid resistance. In the Embase and MEDLINE searches, this was then combined with study design filters for randomised controlled trials (RCTs), non-RCTs and observational studies. The study design filters used were not referenced, however all contained an extensive combination of subject heading terms and free text terms, and the EAG considered them appropriate.
- Animal-only studies were excluded where possible.
- No date or language limits were applied to the searches.
- Search terms were included which attempted to exclude paediatric studies (lines #69-#71; #148-#150; #182-#184 in Tables 2, 3 and 4). Although this was done with caution, there is still the potential for this approach to risk omitting potentially relevant studies due to inaccuracies in database indexing. However, the EAG believes that the extensive searches conducted on multiple resources may have mitigated against this limitation in the search strategy.

3.1.2 Inclusion criteria

A SLR was conducted to identify relevant clinical evidence. Full details of the SLR search strategy, study selection process and results were reported in Appendix D of the CS.[10]

The eligibility criteria used in the search strategy is presented in Table 3.2.

Table 3.2: Eligibility criteria for the SLR

Category	Inclusion criteria	Exclusion criteria
Population	• Male or female adolescent or adult patients (≥12 years)[a] • Patients who have undergone alloSCT, and have been diagnosed with aGvHD (Grades I-IV), or cGvHD (mild-severe) • Patients with GvHD that is steroid refractory[b]/steroid-dependent	• Infants and paediatric patients (<12 years) • Patients who do not have aGvHD or cGvHD • Patients receiving prophylaxis to prevent development of GvHD • Patients with GvHD that is steroid responsive
Intervention	Ruxolitinib (Jakavi® or Jakafi®) Belumosudil (Rezurock®) BAT, including but not limited to: • Anti-thymocyte globulin • Extracorporeal photopheresis • Mesenchymal stromal cells • Regulatory T cells • Faecal microbiota transplantation • Low-dose methotrexate • Mycophenolate mofetil • Calcineurin inhibitors • α1-antitripsin • mTOR inhibitors, including but not limited to: Everolimus, Sirolimus • Monoclonal antibodies, including but not limited to: Infliximab, Rituximab, Alemtuzumab, Basiliximab, Daclizumab, Vedolizumab • TKIs/JAK1 inhibitors, including but not limited to: Ibrutinib, Imatinib • Pentostatin • Etanercept	• Chinese herbal medicines • Alternative medicines
Comparators	Any or none	NA
Outcomes	Efficacy: • Response rate: ORR, CR, PR, VGPR, SD, PD, TTR	Outcomes not listed

Category	Inclusion criteria	Exclusion criteria
	• Mortality: overall mortality, GvHD-related mortality, infection-related mortality, non-relapse mortality, transplant-related mortality • Survival: OS, cGvHD-free survival, FFS • Steroid use: reduction in steroid use, cessation of steroid use Safety: • AEs, SAEs, withdrawal due to AEs • Malignant relapse • Transformation from aGvHD to cGvHD • aGvHD flare, aGvHD relapse • Serious infections • Cytopenia • Cytomegalovirus	
Study design	• RCTs • Non-randomised multi-arm trials • Single-arm trials • Observational studies • Sample size of ≥30 relevant patients[c]	• Case studies/case reports • Narrative reviews • Letters • SLRs/(N)MAs[d] • Sample size of <30 relevant patients[c]
Date limits	• De novo SLR (November 2019) Manuscripts published at any time • First SLR update (September 2021) Manuscripts from 15 November 2019 to present • Second SLR update (January 2024) All records (manuscripts and conference abstracts/posters) from 10 September 2021 to present	• De novo SLR (November 2019) All conference abstracts/posters • First SLR update (September 2021) Manuscripts from before 15 November 2019, and all conference abstracts/posters • Second SLR update (January 2024) Records from before 10 September 2021
Countries	No restrictions	No restrictions
Languages	English language studies	Non-English language studies (includes non-English language publications with an English abstract)

Based on Table 5 of Appendix D of the CS[10]
[a]If the average (mean or median) age of participants was <12, the publication was excluded, unless subgroup data were presented for patients aged ≥12 years.
[b]Where studies reported that patients were refractory to first line therapy, but did not explicitly state the first line therapy, it was assumed that patients with grade II-IV aGvHD and patients with moderate to severe cGvHD had received steroids.
[c]Studies must have had ≥30 aGvHD patients and/or ≥30 cGvHD patients to be included; studies with ≥30 GvHD patients overall but <30 aGvHD patients and <30 cGvHD patients were excluded.

Category	Inclusion criteria	Exclusion criteria
[d]Relevant SLRs/(N)MAs were included at the title/abstract screening stage so their bibliographic reference lists could be handsearched for relevant studies; they were then excluded at the full-text screening stage unless they presented novel data. AEs = adverse events; aGvHD = acute graft-versus-host disease; alloSCT = allogeneic stem cell transplant; BAT = best available therapy; cGvHD = chronic graft-versus-host disease; CR = complete response; FFS = failure-free survival; GvHD = graft-versus-host disease; JAK = Janus kinase; mTOR = mammalian target of rapamycin; NA = not applicable; (N)MA = (network) meta-analysis; ORR = overall response rate; OS = overall survival; PD = progressive disease; PR = partial response; RCT = randomised controlled trial; SAE = serious adverse event; SD = stable disease; SLR = systematic literature review; TKI = tyrosine kinase inhibitor; TTR = time to response; VGPR = very good partial response		

3.1.3 Critique of data extraction

Two reviewers independently reviewed the retrieved records both at title and abstract, and full text screening stages. Any discrepancies between both independent reviewers were initially discussed and then a final decision was made by a third independent reviewer when required. Data were extracted by one reviewer and checked for quality by a second reviewer. No details of resolving discrepancies were provided.

EAG comment: The data extraction process has not followed good practice in systematic reviews.[11] Without duplicate data extraction by two independently reviewers, errors or potential biases may be introduced. The approach used for resolving discrepancies remains unclear.

3.1.4 Quality assessment

The Company conducted the risk of bias assessment of the RCTs using the NICE 7-item checklist.[12] Whereas observational and the single arm trials were not quality-assessed. The process of quality assessment was not reported. Quality assessment is further examined in Section 3.2.4.

EAG comment: A critical appraisal of non-randomised controlled studies is lacking. The company was asked to provide assessment of bias in the included non-randomised studies, to which they responded: *"Risk of bias assessment for single-arm or non-randomised trials, including REACH1, has now been performed using the Downs and Black checklist".*[5]

3.1.5 Evidence synthesis

No indirect treatment comparisons were made as direct trial data comparing ruxolitinib to BAT were available from REACH2.

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The clinical effectiveness Section of the CS presented data from two studies, REACH2 and REACH1. REACH2 is a multicentre randomised, open-label, global Phase 3 study of ruxolitinib (n=154) and BAT (n=155) in patients 12 years of age or older with aGvHD after allogenic stem cell transplant (alloSCT). REACH1 was a multicentre single cohort, open-label phase 2 study of ruxolitinib in combination with corticosteroids in patients with Grades II to IV SR-aGvHD after alloSCT. A comparative summary of both trial methodologies is provided in Table 3.3.

Table 3.3: Comparative summary of trial methodology

	REACH2	REACH1
Location	105 treatment centres across 22 countries	26 treatment centres across the US
Trial design	Multicentre, randomised, open-label, global Phase 3 trial comparing the efficacy and safety of ruxolitinib with the investigator's choice of therapy from a list of nine commonly used options (control) in patients 12 years of age or older who had glucocorticoid-refractory aGvHD after alloSCT	Multicentre, single-cohort, open-label, Phase 2 study of ruxolitinib in combination with corticosteroids in patients (≥12 years old) with Grades II to IV SR-aGvHD
Key inclusion criteria for patients	Aged ≥12 years old at the time of informed consent Had undergone alloSCT from any donor source using bone marrow, PBSCs, or cord blood Clinically diagnosed Grade II to IV aGvHD as per MAGIC guidelines. Evident myeloid and platelet engraftment (confirmed within 48 hours prior to study treatment start): ANC >1,000/mm^3 and platelets ≥20,000/mm^3. Use of growth factor supplementation and transfusion support was allowed.	Aged ≥12 years old at the time of informed consent Had undergone first alloSCT from any donor source using bone marrow, PBSCs, or cord blood Clinically suspected Grade II–IV aGvHD as per MAGIC guidelines. Evidence of myeloid engraftment (e.g., ANC ≥0.5 × 10^9/L for 3 consecutive days if ablative therapy was previously used). Use of growth factor supplementation was allowed.
Key exclusion criteria for patients	Failed prior alloSCT within the past 6 months Received more than one systemic treatment for SR-aGvHD Clinical presentation resembling de novo cGvHD or GvHD overlap syndrome Presented with active uncontrolled infection Presented with relapsed primary malignancy, or patients who were treated for relapse after the alloSCT was performed, or who may require rapid immune suppression withdrawal as pre-emergent treatment of early malignancy relapse. A full list of the inclusion and exclusion criteria is reported in the REACH2 CSR.	Received more than one alloSCT Received more than one systemic treatment in addition to corticosteroids for aGvHD Presence of GvHD overlap syndrome Presence of an active uncontrolled infection Evidence of relapsed primary disease or patients who have been treated for relapse after the alloSCT was performed A full list of the inclusion and exclusion criteria is reported in the REACH1 CSR.
Method of study drug administration	309 patients randomised 1:1 to receive either ruxolitinib (n=154) or BAT (n=155) Ruxolitinib arm	Ruxolitinib 5 mg BID (oral tablets) Dose could be increased to 10 mg BID if haematological parameters were stable and no treatment-related toxicity

	REACH2	REACH1
	Ruxolitinib 10 mg BID (as two 5 mg oral tablets) Within the first 28 days, patients with aGvHD disease progression, or mixed response, or no response, could select new systemic treatment per investigator choice. This was considered a treatment failure, and the patient discontinued study treatment. Ruxolitinib dose reductions or modifications were allowed for safety reasons. Patients responding to treatment were tapered off ruxolitinib as needed, starting no earlier than Day 56. The dose tapering strategy was based on evaluation of the condition of the patient, current dosing regimen and the clinical judgment of the investigator BAT arm. Patients received BAT based on the investigator's best judgment. A new immunosuppressive agent could be added to ruxolitinib or BAT treatment regimen if the patient met the criteria for disease progression, no response, or mixed response, or aGvHD flare	was observed after the first 3 days of treatment After Day 180, ruxolitinib could be tapered if the patient had achieved a CR or VGPR and had discontinued corticosteroids for at least 8 weeks. Dose reductions or modifications of ruxolitinib are permitted based on AEs, clinical evaluation, and laboratory assessments.
Permitted and disallowed concomitant medication	The following medications were permitted: Supportive treatments for management of patients with SR-aGvHD, systemic corticosteroids, CNI, topical corticosteroid therapy, aGvHD prophylaxis medications, antibiotics, anti-infectives, immunisations, additional supportive care measures. The following medications were disallowed: Aspirin, NSAIDs or related medications, concomitant use of another JAK inhibitor, investigational medication, chemotherapeutic agents and/or non-schedules DLI, pre-emergent intervention related to graft failure or haematological disease relapse/progression, Fluconazole at daily doses higher than 200 mg.	The following medications were permitted: GvHD prophylaxis medications, additional supportive care measures, biologic agents for treatment of non-cancer indications. The following medications were disallowed: concurrent anticancer therapy, secondary GvHD therapy due to insufficient response/progression on study treatment, concomitant use of another JAK inhibitor, investigational medication unless approved by medical monitor.
Primary outcomes	ORR at Day 28 after randomisation, defined as the proportion of patients in each arm demonstrating a CR or PR	ORR at Day 28, defined as the proportion of patients demonstrating a response (CR, VGPR, or PR) as per the

	REACH2	REACH1
	without requirement for additional systemic therapies for an earlier progression, mixed response or non-response. Scoring of response was relative to the organ stage at the time of randomisation	CIBMTR modifications to the IBMTR response index at the Day 28 response assessment (± 2 days) and before the start of new anti-aGvHD therapy, if applicable
Secondary outcomes	Durable ORR at Day 56 ORR (CR+PR) at Day 14 DOR was assessed for responders only and was defined as the time from first response until aGvHD progression or the date of additional systemic therapies for aGvHD. Onset of chronic GvHD, or death without prior observation of aGvHD progression are considered as competing risks Weekly cumulative steroid dose for each patient up to Day 56 OS, defined as the time from the date of randomisation to the date of death due to any cause EFS, defined as the time from the date of randomisation to the date of haematological disease relapse / progression, graft failure, or death due to any cause FFS (defined as the time from the date of randomisation to date of haematological disease relapse/progression, NRM, or addition of new systemic aGvHD treatment) NRM, defined as the time from date of randomisation to date of death not preceded by haematological disease relapse/progression Malignancy relapse/progression, defined as the time from date of randomisation to haematological malignancy relapse/progression Incidence of cGvHD, defined as the diagnosis of any cGvHD, including mild, moderate or severe BOR: proportion of patients who achieved OR (CR+PR) at any time point up to and including Day 28 and before the start of any additional systemic therapy for a GvHD PK parameters of ruxolitinib after a single dose and at steady state: C_{max}, AUC_{last}, and AUC_{inf}, C_{trough}, R_{acc} and	6-month DOR (patients still on study completed the Day 180 visit) ORR, defined as the proportion of patients demonstrating a CR, VGPR, or PR at Days 14, 56, and 100 3-month DOR, defined as the time from first response until GvHD progression or death, when all patients who were still on study complete the Day 84 visit) NRM (defined as the proportion of patients who died due to causes other than malignancy relapse at Months 6, 9, 12, and 24) Relapse rate, defined as the proportion of patients whose underlying malignancy relapsed Relapse-related mortality rate, defined as the proportion of patients whose malignancy relapsed and had a fatal outcome FFS (defined as the time from first dose of ruxolitinib to the earliest date that a patient died, had a relapse/progression of the underlying malignancy, required additional therapy for aGvHD, or demonstrated signs or symptoms of cGvHD) OS, defined as the time from study enrolment (first dose of ruxolitinib treatment) to death due to any cause AEs and serious AEs: summaries of clinical safety data (e.g. AEs, infections) were tabulated and listed PK of ruxolitinib when administered in combination with corticosteroids: C_{max}, C_{min}, T_{max}, AUC, and CL/F.

	REACH2	REACH1
	AUC_{tau}; other PK parameters are CL/F, Vz/F, T_{max} and T1/2 Changes in FACT-BMT and in in EQ-5D from baseline to each visit where measured Safety and tolerability including myelosuppression, infections, and bleeding were assessed by monitoring the frequency, duration, and severity of AEs	
Pre-planned subgroup analyses of primary endpoint	Subgroups for the primary efficacy endpoint analysis: Age group Gender Race Region Acute GvHD grade Source of grafts Criteria for SR-aGvHD Prior aGvHD Conditioning regimen Stem cell type Donor HLA status Donor gender match Donor CMV status Donor source/HLA match status aGvHD organ involvement at randomisation	Subgroups for the primary efficacy endpoint analysis: Baseline SR-aGvHD grade Baseline steroid-refractory status Use of immunosuppressant medication and CNIs Average ruxolitinib dose from Day 1 to Day 28 Age group (<65, ≥65 years) Gender Race Baseline organ involvement.

Based on Table 8 of the CS[3]

Based on REACH2 final analysis.

AE = adverse event; aGvHD = acute graft-versus-host disease; alloSCT = allogeneic stem cell transplant; ANC = absolute neutrophil count; AUC = area under the curve; AUCinf = AUC from time zero to infinity; AUClast = AUC from time zero to the last measurable concentration sampling time; AUCtau = AUC calculated to the end of a dosing interval (12 hr) at steady-state; BAT = best available therapy; BID = twice a day; BOR = best overall response; cGvHD = chronic graft-versus-host disease; CIBMTR = Center for International Blood and Marrow Transplant Research; CL/F = apparent clearance of study drug from plasma; Cmax = maximum observed plasma drug concentration; Cmin = minimum observed plasma drug concentration; CMV = cytomegalovirus; CNI = calcineurin inhibitor; CR = complete response; CS = company submission; CSR = Clinical Study Report; Ctrough = observed plasma drug concentration obtained prior to administration of the next dose; DLI = donor lymphocyte infusion; DOR = duration of response; EFS = event-free survival; FFS = failure-free survival; HLA = human leukocyte antigen; IBMTR = International Blood and Marrow Transplant Registry; IV = intravenous; JAK = Janus kinase; MAGIC = Mount Sinai acute GvHD International Consortium; NRM = non-relapse mortality; NSAID = non-steroidal anti-inflammatory drug; ORR = overall response rate; OS = overall survival; PBSC = peripheral blood stem cell; PK = pharmacokinetics; PR = partial response; Racc = accumulation ratio; SR-aGvHD = steroid-refractory acute graft-versus-host disease; SR-cGvHD = steroid-refractory chronic graft-versus-host disease; T1/2 = elimination half-life; Tmax = time of maximum plasma drug concentration; US = United States; VGPR = very good partial response; Vz/F = apparent volume of distribution during terminal phase

3.2.1 Study design

3.2.1.1 REACH2

As previously mentioned, REACH2 was Phase 3, randomised, open-label, multicentre study of ruxolitinib and BAT in patients with steroid-refractory-acute graft-versus-host disease (SR-aGvHD) after alloSCT. There was a total of 309 patients who were randomised 1:1 to receive ruxolitinib (n=154) or BAT (n=155). The investigator identified the BAT in REACH2 prior to patient randomisation among the following treatments used in this setting:

- Anti-thymocyte globulin (ATG)
- ECP
- Mesenchymal stromal cells (MSCs)
- Low-dose methotrexate (MTX)
- Mycophenolate mofetil (MMF)
- Mammalian target of rapamycin (mTOR) inhibitors (everolimus or sirolimus)
- Etanercept
- Infliximab.

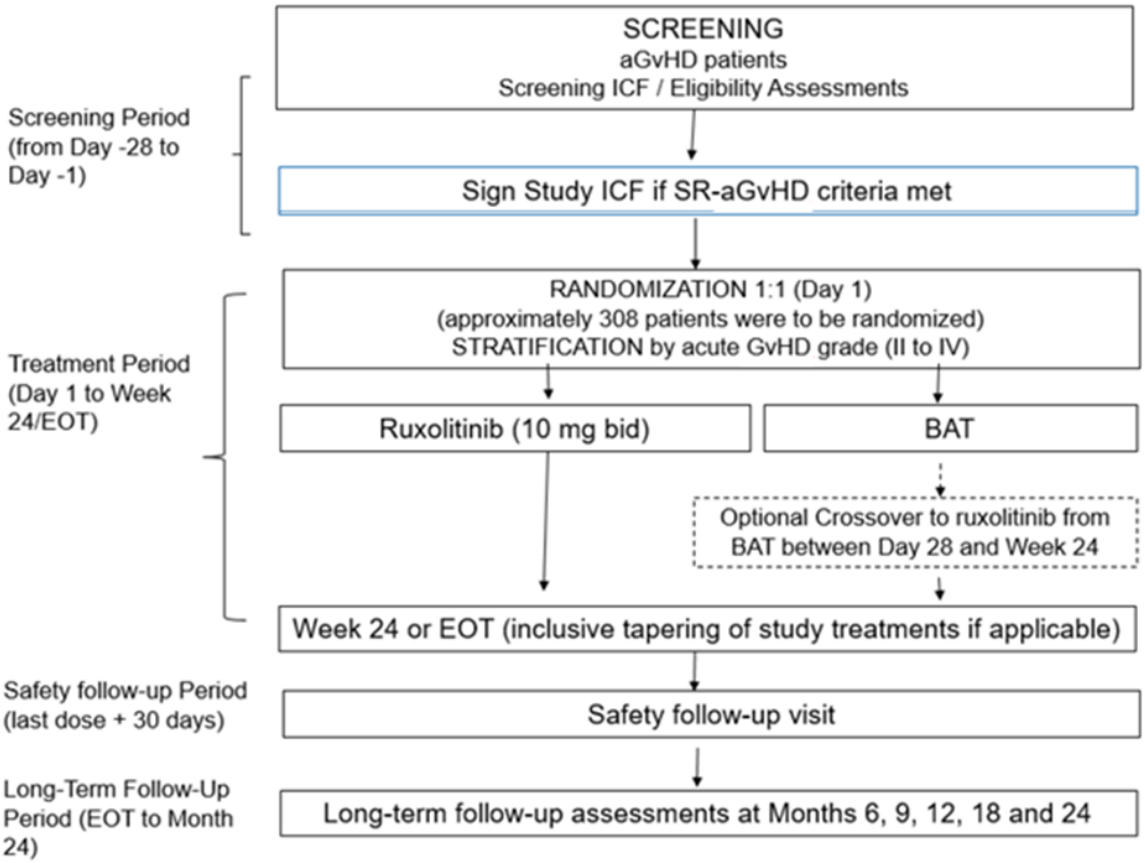
The most common initial BAT, administered to 27.3% was ECP, followed by MMF (16.7%) and etanercept (14.7%). The screening period lasted 28 days up until the day prior to the commencement of treatment, whilst the treatment ranged from day 1 to week 24/end of treatment (EOT). Treatment began on day 1 followed by regular visits for assessments of efficacy and safety. Assessments were performed within 7 days from the last dose. During the treatment period, the CS stated that "*patients randomised to BAT were eligible to cross over to ruxolitinib between Day 28 and Week 24 if they failed to meet the primary endpoint response definition at Day 28 or lost the response thereafter and met criteria for progression, mixed response, or no response, necessitating new additional systemic immunosuppressive treatment for aGvHD and did not have signs/symptoms of cGvHD (overlap syndrome, progressive, or de novo cGvHD)*". Regarding safety, the study included a 30-day safety follow-up visit for all patients after the last dose of ruxolitinib or BAT. Patients were followed up for long-term observation up to 24 months from EOT. More patients in the ruxolitinib arm (35; 22.7%) completed the treatment compared to the BAT arm (20; 12.9%). The most common reasons for discontinuation (ruxolitinib versus BAT arm) were lack of efficacy (20.8% versus 44.5%), death (16.2% versus 14.2%) and AEs (17.5% versus 3.2%). During this period, long term data was collected including:

- Survival
- Any relapse/progression of the underlying haematological disease for which the alloSCT procedure was performed
- Non-relapse mortality (NRM), any occurrence of graft failure
- Event-free survival (EFS), any occurrence of cGvHD
- Occurrence of any second primary malignancies.

Visits for these assessments occurred at 6, 9, 12, 18 and 24 months from randomisation (Day 1).

Figure 3.1 illustrates the study design of REACH2.

Figure 3.1: Study design of REACH2

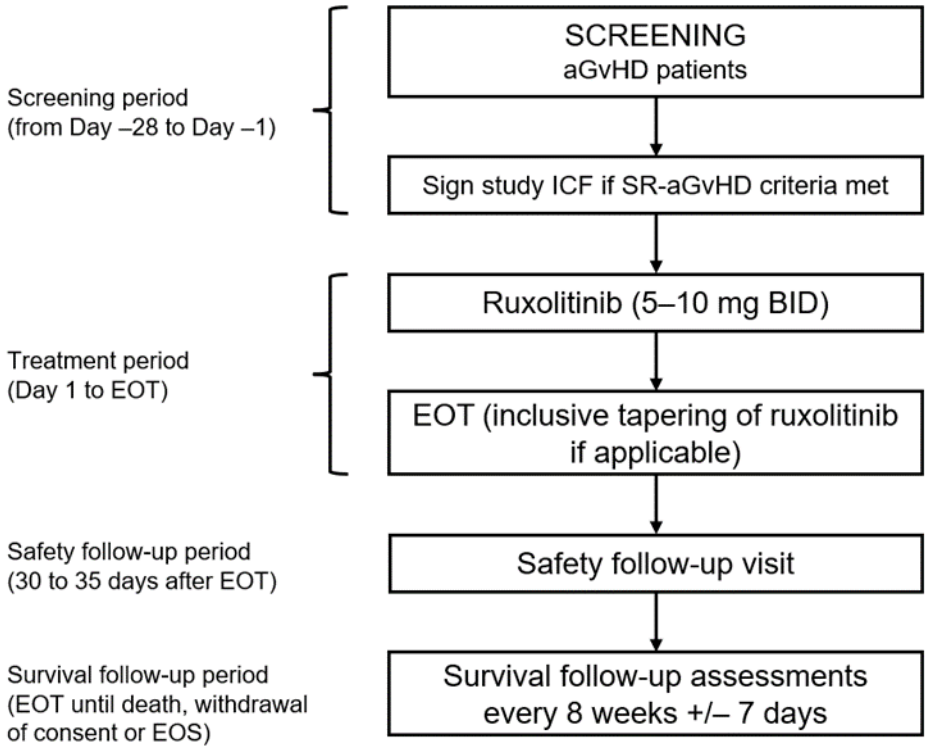


Based on Figure 4 of the CS[3]
aGvHD = acute graft-versus-host disease; BAT = best available treatment; bid = twice a day; CS = company submission; CSR = Clinical Study Report; EOT = end of treatment; ICF = informed consent form; SR-aGvHD = steroid-refractory acute graft-versus-host disease

3.2.1.2 REACH1

As previously mentioned, REACH1 was a phase 2, single cohort, open-label, multicentre study of ruxolitinib in combination with corticosteroids in patients with Grades II to IV SR-aGvHD after alloSCT. A total of 71 patients were treated with 5 mg of ruxolitinib twice a day (BID). The dose was increased to 10 mg BID if haematological parameters were stable, and no treatment-related toxicity was observed after the first 3 days of treatment. The CS stated that "*Study participation was expected to average 12 months: 28 days for screening, approximately 9 months for treatment (length of time estimated for patients to be deriving benefit), 30 to 35 days after treatment ended for safety follow-up, and a survival follow-up period lasting until death, withdrawal of consent, or the end of the study, whichever occurred first*". Of the 71 patients, 68 (95.8%) stopped treatment with 24 patients (33.8%) discontinuing on or before Day 28. Adverse events and physician decision were the most reported reasons for discontinuation. Figure 3.2 illustrates the study design of REACH1.

Figure 3.2: Study design of REACH1



Based on Figure 5 of the CS[3]
aGvHD = acute graft-versus-host disease; BID = twice a day; CS = company submission; EOT = end of treatment; EOS = end of study; ICF = informed consent form; SR-aGvHD = steroid-refractory acute graft-versus-host disease

3.2.2 Baseline characteristics

This subsection will describe the baseline characteristics of patients from both REACH2 and REACH1 studies, respectively.

For REACH2 baseline demographics were well-balanced between ruxolitinib and BAT arms. The mean age for patients in the ruxolitinib arm was 48.1 years (standard deviation [SD]: 16.3) and in the BAT arm was 50.9 years (SD: 14.97). The study had more female patients than males, but the breakdown proportion was similar between treatment arms: ruxolitinib arm: 40.3% female, 59.7% male; BAT arm: 41.3% female, 58.7% male.

For the REACH1 study the majority of patients were less than 65 years with a median age of 58 years and a range 18 -73 years. Gender was evenly distributed, whilst 93% of patients were White/Caucasian.

Table 3.4 present the baseline demographics of patients in both REACH2 and REACH1, respectively.

Table 3.4: Baseline demographic and clinical characteristics – FAS, REACH2 and REACH1

	REACH2		REACH1
	Ruxolitinib n=154	**BAT n=155**	**Ruxolitinib N=71**
Age (years)			
n	154	155	71

	REACH2		REACH1
	Ruxolitinib n=154	**BAT n=155**	**Ruxolitinib N=71**
Mean (SD)	48.1 (16.30)	50.9 (14.97)	52.9 (14.18)
Median	52.5	54.0	58.0
Q1-Q3	32.0–61.0	41.0–63.0	–
Min-max	12.0–73.0	13.0–71.0	18.0–73.0
Age category – n (%)			
Adolescents, 12 – <18 years	5 (3.2)	4 (2.6)	0
18–65 years	128 (83.1)	126 (81.3)	58 (81.7)
≥65 years	21 (13.6)	25 (16.1)	13 (18.3)
Sex			
Female	62 (40.3)	64 (41.3)	35 (49.3)
Male	92 (59.7)	91 (58.7)	36 (50.7)
Race – n (%)			
White	111 (72.1)	102 (65.8)	66 (93.0)
Black or African American	0	1 (0.6)	3 (4.2)
Asian	19 (12.3)	29 (18.7)	2 (2.8)
American Indian or Alaska native	NR	NR	0
Other	8 (5.2)	4 (2.6)	0
Unknown	16 (10.4)	19 (12.3)	0
Ethnicity – n (%)			
Hispanic/Latino	8 (5.2)	12 (7.7)	9 (12.7)
Not Hispanic/Latino	94 (61.0)	88 (56.8)	60 (84.5)
NR	29 (18.8)	36 (23.2)	2 (2.8)
Unknown	23 (14.9)	19 (12.3)	0
Weight (kg)			
n	150	152	71
Mean (SD)	67.5 (14.04)	66.2 (14.78)	78.64 (21.651)
Median	67.7	66.2	75.90
Q1-Q3	58.0–78.0	54.6–74.5	–
Min-max	28.5–97.0	32.9–115.5	46.0–139.0
Height (cm)			
n	148	144	66
Mean (SD)	169.7 (9.86)	170.0 (10.16)	170.2 (10.64)
Median	170.0	170.0	170.0
Q1-Q3	161.9–177.5	163.0–177.0	–
Min-max	128.7–195.0	146.0–200.0	149.0–193.0
Body mass index (kg/m^2)			
n	146	142	66
Mean (SD)	23.4 (4.24)	22.7 (4.15)	26.83 (6.193)
Median	23.3	22.5	25.41

	REACH2		REACH1
	Ruxolitinib n=154	**BAT n=155**	**Ruxolitinib N=71**
Q1-Q3	20.4–26.2	19.9–24.7	–
Min-max	13.5–34.4	13.9–35.7	18.4–46.6
Assessment of performance status – n (%)			
ECOG	NR	NR	70 (98.6)
Missing	NR	NR	1 (1.4)
ECOG performance status – n (%)			
0	NR	NR	3 (4.2)
1	NR	NR	24 (33.8)
2	NR	NR	25 (35.2)
3	NR	NR	17 (23.9)
4	NR	NR	1 (1.4)
Missing	NR	NR	1 (1.4)
Time from diagnosis of aGvHD Grade ≥2 (days)			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min-max	[redacted]	[redacted]	[redacted]
Overall severity of aGvHD at randomisation			
Grade 0	4 (2.6)	1 (0.6)	0
Grade I	2 (1.3)	0	0
Grade II	47 (30.5)	54 (34.8)	22 (31.0)
Grade III	70 (45.5)	67 (43.2)	33 (46.5)
Grade IV	31 (20.1)	33 (21.3)	16 (22.5)
Prior systemic therapy for aGvHD†			
Steroid only	[redacted]	[redacted]	[redacted]
Steroid + CNI	[redacted]	[redacted]	[redacted]
Steroid + CNI + other systemic therapy	[redacted]	[redacted]	[redacted]
Steroid + other systemic therapy	[redacted]	[redacted]	[redacted]

Based on Table 9 of the CS[3]
aGvHD = acute graft-versus-host disease; BAT = best available therapy; CS = company submission; cGvHD = chronic graft-versus-host disease; CNI = calcineurin inhibitor; CSR = Clinical Study Report; ECOG = Eastern Cooperative Oncology Group; FAS = full analysis set; min = minimum; max = maximum; NR = not reported; Q = quartile; SD = standard deviation

EAG comment: The company were asked to provide baseline characteristics by disease for which alloSCT was required for the two trials (REACH1 and REACH2). The company responded by providing two tables. Table 3.5 highlights disease history by treatment for the REACH2 trial, whilst Table 3.6 presents the disease history by treatment for the REACH1 trial.

Table 3.5: Disease history by treatment - REACH2, FAS

Disease history	Ruxolitinib N=165	BAT N=164	All Patients N=329
Primary diagnosis classification-n (%)			
Malignant-leukaemia/MDS	129 (83.8)	121 (78.1)	250 (80.9)
Malignant-lymphoproliferative	18 (11.7)	26 (16.8)	44 (14.2)
Non-malignant	1 (0.6)	5 (3.2)	6 (1.9)
Other	6 (3.9)	3 (1.9)	9 (2.9)
Diagnosis of underlying malignant disease-n (%)			
Acute lymphoblastic leukaemia	25 (16.2)	16 (10.3)	41 (13.3)
AML	58 (37.7)	63 (40.6)	121 (39.2)
Chronic myelogenous leukaemia	6 (3.9)	2 (1.3)	8 (2.6)
Excess blasts 2, developed from Fanconi syndrome	1 (0.6)	0	1 (0.3)
Hodgkin lymphoma	6 (3.9)	2 (1.3)	8 (2.6)
Multiple myeloma	2 (1.3)	5 (3.2)	7 (2.3)
MDS	26 (16.9)	29 (18.7)	55 (17.8)
Non-Hodgkin lymphoma	9 (5.8)	19 (12.3)	28 (9.1)
Other acute leukaemia	4 (2.6)	3 (1.9)	7 (2.3)
Other leukaemia	6 (3.9)	8 (5.2)	14 (4.5)
Other	4 (2.6)	0	4 (1.3)
Diagnosis of underlying non-malignant disease-n (%)			
Histiocytic disorders	0	1 (0.6)	1 (0.3)
Sickle cell disease	1 (0.6)	1 (0.6)	2 (0.6)
Other	0	3 (1.9)	3 (1.0)
Diagnosis of underlying disease other specify-n (%)			
Blastic neoplasm of plasmacytoid dendritic cells	0	1 (0.6)	1 (0.3)
Multiple myeloma and secondary AML	0	1 (0.6)	1 (0.3)
Myelofibrosis	2 (1.3)	0	2 (0.6)
Myeloma	0	1 (0.6)	1 (0.3)
Myeloproliferative neoplasm	1 (0.6)	0	1 (0.3)
Post polycythaemia vera myelofibrosis	1 (0.6)	0	1 (0.3)
Primary myelofibrosis	1 (0.6)	0	1 (0.3)
Septic granulomatosis	1 (0.6)	0	1 (0.3)

Disease history	Ruxolitinib N=165	BAT N=164	All Patients N=329
Time from diagnosis of underlying disease to screening (year)			
n	154	154	308
Mean (SD)	2.16 (3.195)	1.72 (2.170)	1.94 (2.735)
Median	1.04	0.86	0.94
Min-Max	0.2–25.7	0.2–15.1	0.2–25.7
CIBMTR risk assessment-n (%)			
Low	46 (29.9)	46 (29.7)	92 (29.8)
Intermediate	43 (27.9)	48 (31.0)	91 (29.4)
High	61 (39.6)	55 (35.5)	116 (37.5)
Unknown	4 (2.6)	6 (3.9)	10 (3.2)

Based on Table 3 of the response to request for clarification from the EAG[5]

AML = acute myeloid leukaemia; BAT = best available therapy; CIBMTR = Center for International Blood and Marrow Transplant Research; EAG = Evidence Assessment Group; FAS = full analysis set; MDS = myelodysplastic syndrome; min = minimum; max = maximum; SD = standard deviation

Table 3.6: Summary of cancer history – REACH1, efficacy evaluable population

	Ruxolitinib N=71
Number (%) of Subjects with Cancer History	**71 (100)**
Acute myeloid leukaemia	20 (28.2)
Acute lymphoblastic leukaemia	8 (11.3)
Chronic lymphocytic leukaemia	3 (4.2)
Lymphoma	9 (12.7)
Myelodysplastic syndrome	20 (28.2)
Other	11 (15.5)
Time since diagnosis of underlying malignancy (years)	
n	71
Mean (SD)	2.15 (3.288)
Median	1.08
Min–Max	0.3–26.3
Disease status at time of transplant	
Complete response	50 (70.4)
Partial response	8 (11.3)
Stable disease	5 (7.0)
Relapsed/Refractory	6 (8.5)
Unknown	2 (2.8)

Based on Table 4 of the Response to request for clarification from the EAG[5]

EAG = Evidence Assessment Group; Min = minimum; max = maximum; SD = standard deviation

The EAG are satisfied with both of the tables and information provided in response to the question.

3.2.3 Prior and concomitant aGvHD therapies

Details of the prior and concomitant aGvHD therapies are explained in the following subsection.

In the REACH2 trial, all randomised patients (n=309, 100%) received at least corticosteroids (preferred term prednisolone, prednisone and methylprednisolone) as prior therapy. The majority of patients received a combination of prior steroids and other immunosuppressant such as "*"steroids + CNI" ([redacted]) or "steroid + CNI + other aGvHD systemic therapy" (as prophylaxis and/or treatment) ([redacted])".* In the ruxolitinib arm there were [redacted] of patients received only steroids as prior therapy, whilst only [redacted] received steroids as prior therapy in the BAT arm (Table 3.4 – above). A complete breakdown of prior aGvHD therapies by anatomical therapeutic chemical (ATC) class preferred term in REACH2 is presented in Table 3.7 – below.

Table 3.7: Prior aGvHD therapies by ATC class and preferred term – REACH2, FAS

ATC class **Preferred term**	**Ruxolitinib** **N=154** **n (%)**	**BAT** **N=155** **n (%)**
Any ATC class	152 (98.7)	149 (96.1)
ATC not coded	0	3 (1.9)
Extracorporeal photopheresis	0	2 (1.3)
Mesenchymal stromal cells	0	1 (0.6)
Agents for dermatitis, excluding corticosteroids	24 (15.6)	33 (21.3)
Tacrolimus	23 (14.9)	33 (21.3)
Tacrolimus monohydrate	1 (0.6)	0
Bile acid preparations	1 (0.6)	0
Ursodeoxycholic acid	1 (0.6)	0
Calcineurin inhibitors	79 (51.3)	76 (49.0)
Ciclosporin	58 (37.7)	43 (27.7)
Tacrolimus	23 (14.9)	33 (21.3)
Tacrolimus monohydrate	1 (0.6)	0
Corticosteroids	46 (29.9)	36 (23.2)
Hydrocortisone sodium succinate	1 (0.6)	0
Prednisolone	39 (25.3)	31 (20.0)
Prednisolone metasulfobenzoate sodium	3 (1.9)	0
Prednisolone sodium succinate	4 (2.6)	6 (3.9)
Corticosteroids acting locally	76 (49.4)	61 (39.4)
Hydrocortisone butyrate	1 (0.6)	1 (0.6)
Hydrocortisone sodium succinate	1 (0.6)	0
Prednisolone	39 (25.3)	31 (20.0)
Prednisolone metasulfobenzoate sodium	3 (1.9)	0
Prednisone	32 (20.8)	29 (18.7)
Corticosteroids for local oral treatment	40 (26.0)	31 (20.0)
Hydrocortisone sodium succinate	1 (0.6)	0

ATC class **Preferred term**	**Ruxolitinib** **N=154** **n (%)**	**BAT** **N=155** **n (%)**
Prednisolone	39 (25.3)	31 (20.0)
Corticosteroids, combinations for treatment of acne	105 (68.2)	118 (76.1)
Methylprednisolone	83 (53.9)	85 (54.8)
Methylprednisolone sodium succinate	23 (14.9)	39 (25.2)
Corticosteroids, moderately potent (group II)	1 (0.6)	1 (0.6)
Hydrocortisone butyrate	1 (0.6)	1 (0.6)
Corticosteroids, plain	134 (87.0)	125 (80.6)
Hydrocortisone sodium succinate	1 (0.6)	0
Methylprednisolone	83 (53.9)	85 (54.8)
Prednisolone	39 (25.3)	31 (20.0)
Prednisolone metasulfobenzoate sodium	3 (1.9)	0
Prednisolone sodium succinate	4 (2.6)	6 (3.9)
Prednisone	32 (20.8)	29 (18.7)
Corticosteroids, potent (group III)	83 (53.9)	85 (54.8)
Methylprednisolone	83 (53.9)	85 (54.8)
Corticosteroids, weak (group I)	135 (87.7)	138 (89.0)
Hydrocortisone sodium succinate	1 (0.6)	0
Methylprednisolone	83 (53.9)	85 (54.8)
Methylprednisolone sodium succinate	23 (14.9)	39 (25.2)
Prednisolone	39 (25.3)	31 (20.0)
Prednisolone metasulfobenzoate sodium	3 (1.9)	0
Prednisolone sodium succinate	4 (2.6)	6 (3.9)
Glucocorticoids	149 (96.8)	149 (96.1)
Hydrocortisone butyrate	1 (0.6)	1 (0.6)
Hydrocortisone sodium succinate	1 (0.6)	0
Methylprednisolone	83 (53.9)	85 (54.8)
Methylprednisolone sodium succinate	23 (14.9)	39 (25.2)
Prednisolone	39 (25.3)	31 (20.0)
Prednisolone metasulfobenzoate sodium	3 (1.9)	0
Prednisolone sodium succinate	4 (2.6)	6 (3.9)
Prednisone	32 (20.8)	29 (18.7)
Interleukin inhibitors	0	3 (1.9)
Basiliximab	0	3 (1.9)
Other immunosuppressants	0	3 (1.9)
Remestemcel-l	0	3 (1.9)
Other ophthalmologicals	58 (37.7)	43 (27.7)
Ciclosporin	58 (37.7)	43 (27.7)

ATC class Preferred term	Ruxolitinib N=154 n (%)	BAT N=155 n (%)
Protein kinase inhibitors	1 (0.6)	2 (1.3)
Everolimus	1 (0.6)	1 (0.6)
Ruxolitinib	0	1 (0.6)
Selective immunosuppressants	10 (6.5)	9 (5.8)
Anti-thymocyte immunoglobulin	0	1 (0.6)
Anti-thymocyte immunoglobulin (rabbit)	1 (0.6)	1 (0.6)
Everolimus	1 (0.6)	1 (0.6)
Mycophenolate mofetil	7 (4.5)	5 (3.2)
Mycophenolate sodium	1 (0.6)	0
Mycophenolic acid	0	1 (0.6)

Based on Table 2 of Appendix M

Based on REACH2 final analysis CSR (2).

A medication/therapy can appear in more than one ATC class.

aGvHD = acute graft-versus-host disease; ATC = anatomical therapeutic chemical; BAT = best available therapy; CSR = Clinical Study Report; FAS = full analysis set

From randomisation up to EOT, 98.7% and 100% of patients consumed concomitant medications in the ruxolitinib and BAT arms. The CS stated that *"The overall profile of concomitant medications was similar between the two treatment arms, with a few minor differences. In addition to corticosteroids and CNIs, the frequent concomitant medications also included agents for treatment of infections, gastric motility enhancers and electrolytes. With regards to immunosuppressive treatment, 85.5% and 82.0% of patients in the ruxolitinib and in the BAT arms, respectively, received CNIs from the time of randomisation. The most frequent CNI was cyclosporin (61.2% and 54.7%)."*[3]

In REACH1 all patients (n=71, 100%) received prior systemic therapy with corticosteroids, which included methylprednisolone, methylprednisolone sodium succinate, and prednisone. Additional, prior systemic corticosteroids for GvHD in more than one patient included budesonide and triamcinolone. A complete breakdown of prior aGvHD therapies by ATC class preferred term in REACH2 is presented in Table 3.8.

Table 3.8: Prior aGvHD therapies by ATC class and preferred term – REACH1, efficacy evaluable set

ATC class Preferred term	Ruxolitinib N=71 n (%)
Patients who received prior aGvHD therapy	71 (100.0)
Calcineurin inhibitors	17 (23.9)
Ciclosporin	3 (4.2)
Tacrolimus	14 (19.7
Corticosteroids acting locally	7 (9.9)
Budesonide	7 (9.9)
Corticosteroids, moderately potent (group II)	3 (4.2)

ATC class **Preferred term**	**Ruxolitinib** **N=71** **n (%)**
Triamcinolone	3 (4.2)
Corticosteroids, very potent (group IV)	1 (1.4)
Clobetasol	1 (1.4)
Corticosteroids, weak (group I)	1 (1.4)
Hydrocortisone	1 (1.4)
Folic acid analogues	8 (11.3)
Methotrexate	7 (9.9)
Methotrexate sodium	1 (1.4)
Glucocorticoids	71 (100.0)
Beclometasone dipropionate	7 (9.9)
Methylprednisolone	58 (81.7)
Methylprednisolone sodium succinate	7 (9.9)
Prednisone	41 (57.7)
Gonadotropins	1 (1.4)
Chorionic gonadotrophin	1 (1.4)
Interleukin inhibitors	1 (1.4)
Basiliximab	1 (1.4)
Other antihistamines for systemic use	1 (1.4)
Hydroxyzine hydrochloride	1 (1.4)
Other therapeutic products	1 (1.4)
Psoralens for systemic use	1 (1.4)
Methoxsalen	1 (1.4)
Selective immunosuppressants	10 (14.1)
Abatecept	2 (2.8)
Antithymocyte immunoglobulin (rabbit)	1 (1.4)
Mycophenolate mofetil	3 (4.2)
Sirolimus	2 (2.8)
Vedolizumab	2 (2.8)
Tumour necrosis factor alpha (tnf-) inhibitors	1 (1.4)
Etanercept	1 (1.4)

Based on Table 3 of Appendix M
Based on REACH1 final analysis CSR (4).
aGvHD = acute graft-versus-host disease; ATC = anatomical therapeutic chemical; CSR = Clinical Study Report

All participants took at least one concomitant medication. Nucleosides and nucleotides excluding reverse transcriptase inhibitors (n=69, 97.2%), calcineurin inhibitors (CNIs) (n=63, 88.7%), and proton pump inhibitors and electrolyte solutions (n=60, 84.5% each), were the most frequently prescribed classes of concomitant medications.

EAG comment: The EAG asked the company to provide a complete list of treatment and precise combinations of treatments in the BAT arm of REACH2 with the percentage of patients who receive them. In the company response to the Clarification Questions, the company state that, *"as part of the REACH2 exclusion criteria patients were not permitted to receive more than one systemic treatment for SR-aGvHD, therefore there were no treatment combinations."* The company did however state that there were some concomitant medications that were permitted, including systemic therapies if used for aGvHD prophylaxis only. The company directed the EAG to pages 127-128 of the REACH final analysis Clinical Study Report (CSR) for a full list of concomitant therapies in ruxolitinib and BAT arms with the REACH2 trial. The company also provided a table summarising the permitted and disallowed medications from REACH2, this has been provided earlier in Table 3.3. The EAG notes that there did not appear to be any substantial differences between the arms of the REACH2 trial.

3.2.4 Efficacy results of the included studies

3.2.4.1 REACH2

3.2.4.1.1 Overall response rate at Day 28

Section B.2.6 of the CS[3] included the following statements: *"REACH2 met its primary endpoint: ORR at Day 28 was higher in the ruxolitinib arm (62.3%) than in the BAT arm (39.4%). There was a statistically significant difference between the treatment arms (stratified Cochrane-Mantel-Haenszel (CMH) test p<0.0001, one-sided, odds ratio: 2.64 with 95% confidence interval [CI]: 1.65, 4.22)."* Further details are shown in Table 3.9 below.

The company further confirmed (in Section B.2.6 of the CS[3] that, *"Sensitivity analysis performed using the Fisher's exact method confirmed the results of the primary analysis, with an odds ratio of 2.55 (95% CI: 1.61, 4.03; p<0.0001)."*

Table 3.9: Summary of ORR at Day 28 – REACH2, primary analysis, FAS

	Ruxolitinib N=154	**BAT N=155**
Responders, n (%)		
CR	53 (34.4)	30 (19.4)
PR	43 (27.9)	31 (20.0)
Non-responders, n (%)		
No response	7 (4.5)	10 (6.5)
Mixed response[†]	10 (6.5)	17 (11.0)
Progression	4 (2.6)	13 (8.4)
Other[‡]	1 (0.6)	7 (4.5)
Unknown/missing	36 (23.4)	47 (30.3)
Death	15 (9.7)	22 (14.2)
Early discontinuation	17 (11.0)	16 (10.3)
Missing visits	4 (2.6)	9 (5.8)
ORR: CR + PR, n (%)	**96 (62.3)**	**61 (39.4)**
95% CI	54.2, 70.0	31.6, 47.5
Odds ratio (95% CI)	2.64 (1.65, 4.22)	
p-value	<0.0001	

	Ruxolitinib N=154	BAT N=155
Based on Table 12 of the CS[3] †Defined as improvement of at least 1 stage in the severity of GvHD in at least one organ accompanied by progression in another organ or development of signs or symptoms of GvHD in a new organ. ‡Patients with additional systemic therapies along with CR/PR per investigator assessment. BAT = best available therapy; CI = confidence interval; CR = complete response; CS = company submission; FAS = full analysis set; GvHD = graft-versus-host disease; ORR = overall response rate; PR = partial response		

3.2.4.1.2 Durable ORR at Day 56

In Section B.2.6 of the CS[3] the company explained that, "*Durable ORR at Day 56 as of the primary analysis cut-off, showed a statistically significant difference between the two arms and was in favour of ruxolitinib (39.6% in the ruxolitinib arm vs 21.9% in the BAT arm; odds ratio: 2.38; 95% CI: 1.43, 3.94; p=0.0005).*" Further details are shown in Table 3.10 below.

Table 3.10: Durable ORR at Day 56 – REACH2, primary analysis, FAS

	Ruxolitinib N=154	BAT N=155
Responders, n (%)		
CR	41 (26.6)	25 (16.1)
PR	20 (13.0)	9 (5.8)
Non-responders, n (%)		
No response	1 (0.6)	1 (0.6)
Mixed response†	5 (3.2)	4 (2.6)
Progression	0	0
Other‡	0	1 (0.6)
Unknown/missing	29 (18.8)	21 (13.5)
Death	7 (4.5)	2 (1.3)
Early discontinuation	13 (8.4)	15 (9.7)
Missing visits	9 (5.8)	4 (2.6)
ORR: CR + PR, n (%)	**61 (39.6)**	**34 (21.9)**
95% CI	(31.8, 47.8)	(15.7, 29.3)
Odds ratio (95% CI)	2.38 (1.43,3.94)	
p-value	0.0005	
Based on Table 13 of the CS[3] †Defined as improvement of at least 1 stage in the severity of GvHD in at least one organ accompanied by progression in another organ or development of signs or symptoms of GvHD in a new organ. ‡Patients with additional systemic therapies along with CR/PR per investigator assessment. BAT = best available therapy; CR = complete response; CS = company submission; CSR = Clinical Study Report; FAS = full analysis set; GvHD = graft-versus-host disease; ORR = overall response rate; PR = partial response		

3.2.4.1.3 Best overall response

In Section B.2.6 of the CS[3] the company reported that, "*The best overall response (BOR) up to Day 28 was higher in the ruxolitinib arm (81.8%; 95% CI: 74.8, 87.6) than in the BAT arm (60.6%; 95% CI: 52.5, 68.4).*"

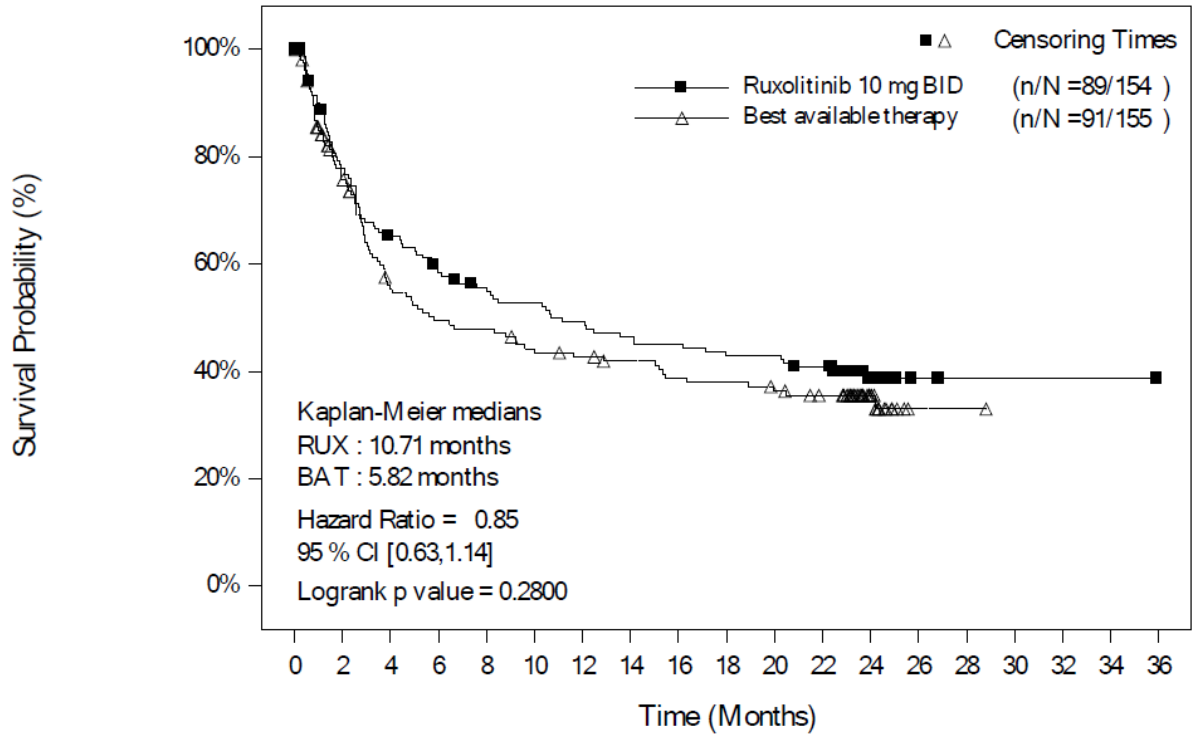
3.2.4.1.4 Duration of response

The company reported the following: *"The median duration of response (DOR) was longer in the ruxolitinib arm (167 days, range: 22 to 677) than in the BAT arm (106 days, range: 10–526)."* [3]

3.2.4.1.5 Overall survival

Section B.2.6 of the CS[3] included the following statements: "*The Kaplan-Meier (KM)-estimated median OS was longer in the ruxolitinib arm (10.71 months) than in the BAT arm (5.82 months). There was a 15% reduction in the risk of death in the ruxolitinib arm relative to the BAT arm (HR: 0.85; 95% CI: 0.63, 1.14), although not statistically significant (log-rank p-value: 0.2800)*" Further details are shown in Figure 3.3 below.

Figure 3.3: Kaplan-Meier curves of OS – REACH2, final analysis, FAS



No. of patients still at risk

Time(Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36
Ruxolitinib 10 mg BID	154	116	96	85	79	75	70	66	64	61	61	57	24	2	1	1	1	1	0
Best available therapy	155	107	75	67	65	58	56	53	49	48	45	41	17	1	1	0	0	0	0

Based on Figure 6 of the CS[3]
BAT = best available therapy; BID = twice a day; CI = confidence interval; CS = company submission; FAS = full analysis set; OS = overall survival; RUX = ruxolitinib

In the REACH2 clinical trial, 49 patients in the BAT arm (32%) crossed over to the ruxolitinib treatment during the randomised treatment period. This crossover can bias the estimates of outcomes such as time

to relapse, death, and cGvHD. To account for this, the company used the two-stage method recommended in NICE Decision Support Unit (DSU) technical support document (TSD) 16 to adjust survival times for treatment switching.[3]

According to Appendix O,[13] a secondary baseline was established at the time of treatment failure, and survival post-failure was modelled using Accelerated Failure Time (AFT) models. These models included covariates like switching to ruxolitinib, age, sex, race, and the grade of GvHD at baseline. Among several statistical models tested (log-logistic, log-normal, Weibull, and generalised gamma), the generalised gamma model was selected for the base-case due to its best fit. This produces a treatment effect for ruxolitinib in patients who switch, and counterfactual survival times were then generated for each patient by shrinking their post-failure survival using this AFT coefficient. Once counterfactual survival has been estimated, transition probabilities are analysed using standard methods, as per the unadjusted data. Transition probabilities were generated using the time from new systemic therapy to relapse, death or cGvHD and time from relapse to death in REACH2. The following Table 3.11 summarise the models used for crossover adjustment. Figure 3.4 presents observed and counterfactual outcomes from REACH2.

Table 3.11: Crossover adjustment models, REACH2

	OS			IMR			cGvHD		
	Coefficient	SE	p	Coefficient	SE	p	Coefficient	SE	p
Crossover	[redacted]								
Age	[redacted]								
Male	[redacted]								
Black or African American	[redacted]								
Other	[redacted]								
Unknown	[redacted]								
White	[redacted]								
Grade 3	[redacted]								
Grade 4	[redacted]								
Constant	[redacted]								
ln(sigma)	[redacted]								

Based on Table 2 of the Appendix O[13]
cGvHD = chronic graft-versus-host disease; IMR = incidence of malignancy relapse; OS = overall survival; SE = standard error

Figure 3.4: Observed and counterfactual OS in REACH2

Based on Figure 1 of the Appendix O[13]
OS = overall survival

The company reported the following results, "*In the BAT arm, median OS adjusted for crossover was* [redacted] *months, resulting in an adjusted HR of* [redacted] *(95% CI:* [redacted]*), or* [redacted] *in the risk of death in the ruxolitinib arm vs the BAT arm,* [redacted] *(log-rank p-value:* [redacted]*).*"[3] The relevant details are shown in Figure 3.5 below.

Figure 3.5: OS curves adjusted for crossover – REACH2, final analysis, FAS

Based on Figure 7 of the CS[3]

BID = twice a day, CS = company submission; FAS = full analysis set; OS = overall survival

EAG comments: The company reported both the unadjusted result and crossover adjustment result. The crossover adjustment result showed a [redacted] in the risk of death in the ruxolitinib arm relative to the BAT arm (HR: [redacted]; 95% CI: [redacted]) while the unadjusted result showed a 15% reduction in the risk of death with hazard ratio (HR) of 0.85 (95% CI: 0.63, 1.14). The comparison of results shown that the crossover-adjustment is more favourable to ruxolitinib, which is in line with the EAG expectation.

3.2.4.1.6 Failure-free survival

In Section B.2.6 of the CS[3], the company outlined the following: "*Median FFS with ruxolitinib was statistically significantly longer than with BAT (4.86 months vs 1.02 months; HR: 0.51, 95% CI: 0.39, 0.66; p<0.0001)*" The relevant details are shown in Figure 3.6 below.

Figure 3.6: Kaplan-Meier plot of FFS – REACH2, final analysis, FAS

Based on Figure 8 of the CS[3]
BAT = best available therapy; BID = twice a day; CI = confidence interval; CS = company submission; FAS = full analysis set; FFS = failure-free survival; RUX = ruxolitinib

3.2.4.1.7 Incidence of malignancy relapse/progression

The company reported the following: "*Among the 147 patients in each treatment arm who had malignant haematological disease at baseline, events of malignancy relapse/progression occurred in a similar proportion of patients in both treatment arms (13.6% in the ruxolitinib arm and 17.0% in the BAT arm) at the end of study.*"[3] Further details are presented in Figure 3.7 below.

Figure 3.7: Cumulative incidence curve of malignancy relapse/progression– REACH2, final analysis, FAS

Based on Figure 9 of the CS[3]
BID = twice a day; CS = company submission; FAS = full analysis set; NA = not available

3.2.4.1.8 Non-relapse mortality

In Section B.2.6 of the CS[3] the company reported that, "*The cumulative incidence curves for NRM were overlapping for the ruxolitinib and BAT arms, indicating similar event rates between the arms over time.*" The relevant details are shown in Figure 3.8 below.

Figure 3.8: Cumulative incidence curve of NRM – REACH2, final analysis, FAS

Based on Figure 10 of the CS[3]
BID = twice a day; CS = company submission; FAS = full analysis set; NA = not applicable; NRM = non-relapse mortality

3.2.4.1.9 Patient-reported outcomes

The company reported the following: "*In both the randomised treatment and crossover periods,* [redacted]."[3]

3.2.4.1.10 Cumulative steroid dosing

In Section B.2.6 of the CS[3] the company explained that, *"At Day 56, more patients in the ruxolitinib arm (22.1%; 95% CI: 15.8, 29.5) had completely tapered off corticosteroids than in the BAT arm (14.8%; 95% CI: 9.6, 21.4) with an odds ratio of 1.63 (95% CI: 0.91, 2.92)."*

The company also added *"The trend seen at Day 56 continued until EOT. More patients in the ruxolitinib arm (43.5%; 95% CI: 35.5, 51.7) had completely tapered off corticosteroids than in the BAT arm (31.6%; 95% CI: 24.4, 39.6) with odds ratio of 1.67 (95% CI: 1.05, 2.65)."*

3.2.4.1.11 Event-free survival

In Section B.2.6 of the CS[3] the company explained that, "*The KM-estimated median EFS was longer in the ruxolitinib arm (8.28 months) than in the BAT arm (4.17 months). There was a 15% reduction in risk of EFS event in the ruxolitinib arm relative to the BAT arm (HR: 0.85; 95% CI: 0.64, 1.13), which was not statistically significant (log-rank p-value:* [redacted]*).*" Further details are presented in Figure 3.9 below.

Figure 3.9: Kaplan-Meier curves of EFS – REACH2, final analysis, FAS

Based on Figure 11 of the CS[3]
BAT = best available therapy; BID = twice a day; CI = confidence interval; CS = company submission; EFS = event-free survival; FAS = full analysis set; RUX = ruxolitinib

3.2.4.1.12 Incidence of cGvHD

In Section B.2.6 of the CS[3] the company reported that, "*Up to the end of study, 33.8% of patients in the ruxolitinib arm and 21.9% of patients in the BAT arm had developed cGvHD. The proportion of patients with competing risks was similar between the ruxolitinib arm (51.9%) and the BAT arm (54.8%).*"

The company also explained that "*The estimated cumulative incidence rate of cGvHD increased with time in both treatment arms. At 6 months, the probability of cGvHD was [redacted] (95% CI: [redacted] in the ruxolitinib arm and [redacted] 95% CI: [redacted] in the BAT arm). However, in the subsequent timepoints at 12 months, 18 months and 24 months, the probability of cGvHD was [redacted] in the ruxolitinib arm than in the BAT arm ([redacted] vs [redacted], [redacted] vs [redacted] and [redacted] vs [redacted], respectively).*" Further details are presented in Figure 3.10 below.

Figure 3.10: Cumulative incidence of cGvHD – REACH2, final analysis, FAS

Based on Figure 12 of the CS[3]
BID = twice a day; cGvHD = chronic graft-versus-host disease; CS = company submission; FAS = full analysis set; NA = not applicable

3.2.4.1.13 Exploratory efficacy results

Section B.2.6 of the CS[3] included the following statements: "*The proportion of patients who initiated study treatment while being hospitalised was similar between the two treatment arms. The proportion of patients who were re-admitted to hospital (bone marrow transplant unit) was* [redacted] *(ruxolitinib arm:* [redacted]*% and BAT arm:* [redacted]*%).*"

EAG comment: Based on the EAG's discussion in Section 2, the results are further complicated by the difference in ECP utilisation between the REACH2 trial (27%), UK Clinical Practice (46%), and the relevant clinical experts' opinion that most patients will be considered for ECP (see Appendix 1). If ECP is indeed more effective than other BAT therapies, as some evidence suggests,[8] then the lower representation of ECP in the trial could skew the overall effectiveness of ruxolitinib when compared to BAT in favour of ruxolitinib. This discrepancy could result in an inaccurate assessment of ruxolitinib's true effectiveness and cost effectiveness in real-world settings, particularly in the UK. The EAG did request in the clarification letter that, in line with Sections 2.1 and 2.2, that the company discuss the implications of differences between BAT in the trial and ECM in UK clinical practice, to which they responded: *"Figure 14 of the CS showing FFS by the different BAT was presented to UK clinical experts who agreed that the efficacy is comparable among all the treatments and is consistent with clinical experience. Therefore, the clinical experts confirmed there were no major differences between UK established clinical management (ECM) and BAT in REACH2 in terms of prognosis and treatment*

effect, and adjusting the proportions of patients who receive each BAT to reflect a difference in costs was appropriate." (p. 17) The EAG have reproduced Figure 14 in Figure 3.11. It appears to show that ECP is at least one of the most effective three treatments and that the other two of these, everolimus and low-dose methotrexate were only given to 1% and 3% of patients respectively (see Table 20, CS).[3] The company also provided a similar figure for OS (see Figure 3.12). where again ECP seems to be one of the most or the most effective treatment. Therefore, it is plausible that, if more patients had received ECP then the efficacy of BAT might have been higher.

Figure 3.11: FFS by BAT in REACH2

Based on Figure 14, CS[3]
ATG = anti-thymocyte globulin; BAT = best available therapy; CS = company submission; ECP = extracorporeal photopheresis; FFS = failure-free survival; MMF = mycophenolate mofetil; MSC = mesenchymal stromal cells; MTX = methotrexate

Figure 3.12: OS by BAT in REACH2

Based on Figure 8, response to clarification letter[5]
ATG = anti-thymocyte globulin; BAT = best available therapy; ECP = extracorporeal photopheresis; MMF = mycophenolate mofetil; MSC = mesenchymal stromal cells; MTX = methotrexate; OS = overall survival

Of course, this does beg the questions as to why so few patients received ECP when treatment was given according to investigator choice, so the EAG also asked for the criteria and whether there was a lack of access to ECP. The company responded that: *"…patients received BAT based on the investigator's best judgment, taking into account several factors including the manufacturer's instructions, labelling, patient's medical condition, institutional guidelines for any dose adjustment, risk of infection, prior clinical experience, as well as access to the chosen BAT. Status of haematological stability and venous access was not explicitly required for separate consideration, although these factors may have been considered through assessment of 'patient's medical condition' and / or institutional guidelines."* (p.20) They also stated that: *"…there is a possibility that some patients experienced a lack of access to ECP."* (p.20) It is therefore plausible that either the clinician did not realise that ECP might be more effective than most of the other treatments or that they were unable to prescribe it.

On the other hand, the crossover between treatments within the trial introduces additional bias, potentially favouring the comparator treatments. While crossover adjustments can be made, the extent to which they reduce this bias is uncertain. This uncertainty could affect the reliability of survival estimates and other outcome measures, potentially leading to incorrect conclusions about the relative benefits of ruxolitinib. Note that crossover might have the opposite effect on incidence of cGvHD given that increased reduced mortality/increased OS might make the incidence higher.

The EAG therefore continues to recommend that separate results be presented for ruxolitinib versus each of the comparators, at least versus ECP.

3.2.4.2 REACH1

3.2.4.2.1 Overall response rate at Day 28

In Section B.2.6 of the CS[3] the company reported that, "*The study achieved the predetermined threshold for a positive study outcome (lower limit of the 95% CI for Day 28 ORR ≥40%), with 56.3% of patients (95% CI: 44.0, 68.1) demonstrating a response at Day 28, including 26.8% of patients who achieved a CR and 8.5% of patients who achieved a VGPR*." The relevant details are shown in Table 3.12 below.

Table 3.12: Summary of ORR at Day 28 – REACH1, final analysis, efficacy evaluable population

	Ruxolitinib N=71
Responders, n (%)	
CR	19 (26.8)
PR	6 (8.5)
VGPR	15 (21.1)
Non-responders, n (%)	
No response	2 (2.8)
Mixed response†	3 (4.2)
Progression	2 (2.8)
Other‡	1 (1.4)
Unknown/missing	23 (32.4)
Death	10 (14.1)
Early discontinuation	12 (16.9)
Missing visits	1 (1.4)
ORR: CR + PR, n (%)	40 (56.3)
95% CI	(44.0, 68.1)

Based on Table 14 of the CS[3]
†Defined as improvement of at least 1 stage in the severity of GvHD in at least one organ accompanied by progression in another organ or development of signs or symptoms of GvHD in a new organ.
‡Patients with additional systemic therapies along with CR/PR per investigator assessment.
CI = confidence interval; CR = complete response; CS = company submission; GvHD = graft-versus-host disease; ORR = overall response rate; PR = partial response; VGPR = very good partial response

3.2.4.2.2 Duration of response at 6 months

The company reported the following: "*For patients who had a response at any timepoint, median DOR at 6 months was 345 days (95% CI: 154.0, NE).*" The relevant details are shown in Table 3.13 below.

Table 3.13: DOR at 6 months – REACH1, final analysis, efficacy evaluable population

	Ruxolitinib N=71	
	Response at any time point	**Response at Day 28**
Patients who had a response at the specified time point, n (%)	54 (76.1)	40 (56.3)
Patients with events, n (%)	**23 (42.6)**	**16 (40.0)**
Progression of disease	7 (13.0)	5 (12.5)
Death	16 (29.6)	11 (27.5)
Duration of response, days (95% CI)		
25th percentile	96.0 (29.0, 159.0)	154.0 (29.0, 326.0)
50th percentile (median)	345.0 (154.0, NE)	669.0 (159.0, NE)
75th percentile	NE (669.0, NE)	NE (669.0, NE)
Event-free probability estimates at 6-month (95% CI)	62.1 (45.8, 74.8)	68.2 (49.6, 81.2)
Follow-up time, days		
Median	128.5	195.0
Min, max	3.0, 805.0	7.0, 805.0

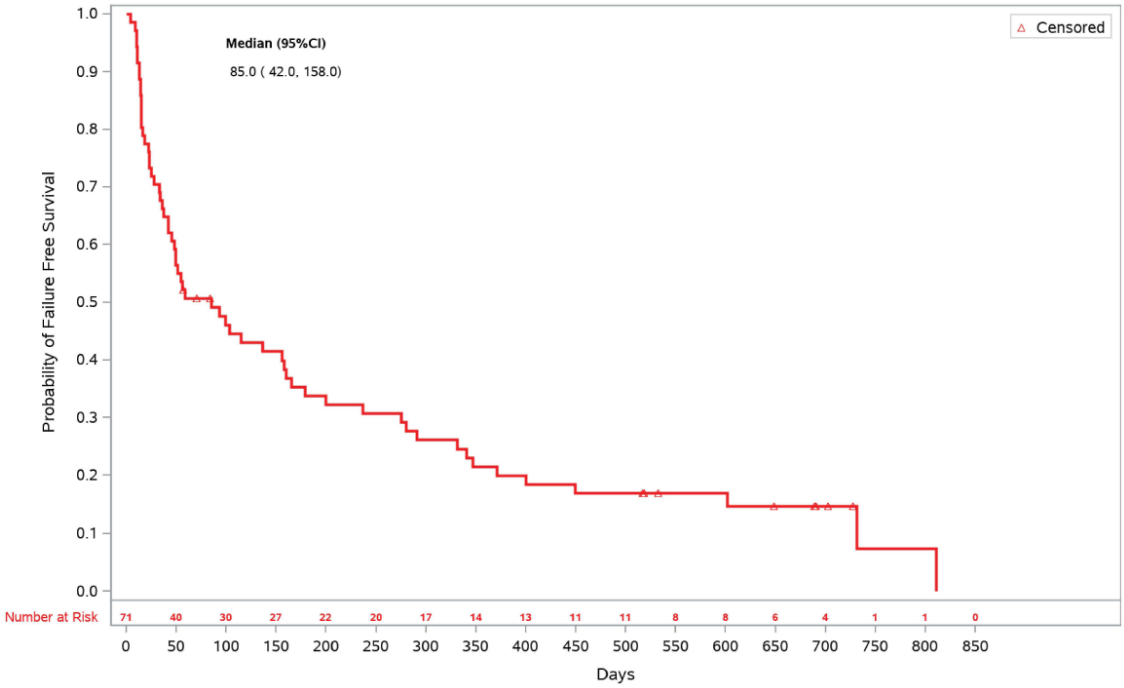
Based on Table 15 of the CS[3]

CI = confidence interval; CS = company submission; DOR = duration of response; min = minimum; max = maximum; NE = not estimated

3.2.4.2.3 Failure-free survival

In Appendix N[14], the company reported the following: "*The median failure-free survival (FFS) time was 85.0 days (95% CI: 42.0, 158.0).*" The relevant details are shown in Figure 3.13 below.

Figure 3.13: Kaplan-Meier estimates of failure-free survival – REACH1, final analysis, efficacy evaluable population



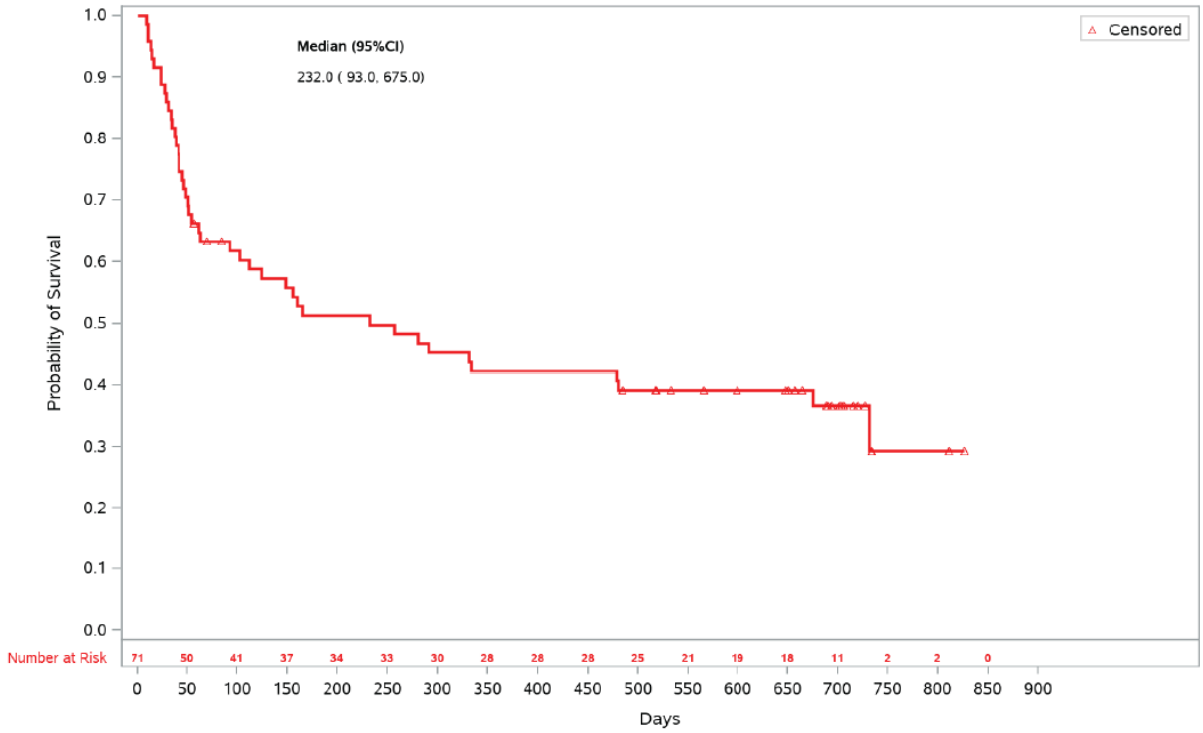
Based on Figure 2 of the Appendix N[14]
CI = confidence interval

EAG comments: The EAG noticed that the median FFS time in REACH1 was 85.0 days (2.80 months), which was lower compared to the result of median FFS with ruxolitinib in REACH2, which was 4.86 months. This may be an issue that needs to be considered.

3.2.4.2.4 Overall survival

In Appendix N[14], the company reported the following: "*The median overall survival (OS) time was 232.0 days (95% CI: 93.0, 675.0).*" The relevant details are shown in Figure 3.14 below.

Figure 3.14: Kaplan-Meier estimates of overall survival (efficacy evaluable population)



Based on Figure 3 of the Appendix N[14]
CI = confidence interval

EAG comments: The EAG noticed that the median overall survival time in REACH1 was 232.0 days (7.63 months), which is lower compared to the result of median OS with ruxolitinib in REACH2, which was 10.71 months. This may be an issue to consider.

3.2.5 Adverse events

The company stated that across REACH2 and REACH1, ruxolitinib was generally well-tolerated in patients with SR-aGvHD. In general, the safety profile of ruxolitinib was consistent with that previously observed in patients with myelofibrosis and polycythaemia vera, and no unexpected toxicities were observed with ruxolitinib therapy, with the assigned dose of 10 mg BID tolerable.

3.2.5.1 REACH2

3.2.5.1.1 Overview of adverse events

The company outlined that, there was a significant difference in duration of exposure between the two treatment groups (median exposure: 63 days (range: 6.0–678.0) in the ruxolitinib arm versus 29 days (range: 1.0–188.0) in the BAT arm, partly because patients on BAT were allowed to cross over to ruxolitinib after Day 28 and there were higher discontinuations during the treatment period in the BAT arm (87.1%) than in the ruxolitinib arm (77.3%). Therefore, the adverse events (AE) profile in the ruxolitinib arm is reflective of the longer treatment duration. Due to that expected imbalance in exposure, safety summaries for the randomised treatment were produced for the following periods, unless specified: up to Day 31 (the upper bound of the Day 28 visit window) and up to either cut-off date, or end date of on-randomised-treatment period, whichever was earlier.

Up to Day 28, a [redacted] (ruxolitinib versus BAT) experienced at least one AE ([redacted] versus [redacted]. The incidence of all AEs, serious AEs (SAE), fatal SAEs and AEs requiring additional therapies was [redacted]. The incidence of treatment-related AEs, AEs leading to discontinuation and AEs leading to dose adjustment/interruption were [redacted] in the ruxolitinib arm than in the BAT arm (Table 3.14).

In the randomised treatment period, [redacted] experienced at least one AE ([redacted]% vs [redacted]%). The overall AE profile during the randomised treatment period remained consistent with that at Day 28 except for SAEs that were [redacted] in the ruxolitinib arm ([redacted]%) than in the BAT arm ([redacted]%)

Table 3.14: Overview of AEs– REACH2, final analysis, safety set

	Up to Day 28				Randomised treatment period			
	Ruxolitinib N=152		BAT N=150		Ruxolitinib N=152		BAT N=150	
	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
All AEs	[redacted]							
Treatment-related	[redacted]							
SAEs	[redacted]							
Treatment-related	[redacted]							
Fatal SAEs	[redacted]							
Treatment-related	[redacted]							
AEs leading to discontinuation	[redacted]							
Treatment-related	[redacted]							
AEs leading to study treatment dose adjustment / interruption	[redacted]							
AEs requiring additional therapy	[redacted]							

Based on Table 16 of CS[3]
AE = adverse event; BAT = best available therapy; CS = company submission; SAE = serious adverse event

3.2.5.1.2 Adverse events suspected to be related to study treatment

During the randomised treatment period, in the ruxolitinib arm, the most frequent AEs by preferred term (PT) (all grades) suspected to be related to study treatment (in ≥5% of patients) were those of

cytopenia, including thrombocytopenia ([redacted]%), anaemia ([redacted]%), platelet count decreased ([redacted]%), neutropenia ([redacted]%), white blood cell (WBC) count decreased ([redacted]%), neutrophil count decreased ([redacted]%), leukopenia ([redacted]%), as well as cytomegalovirus (CMV) infection (combined for PTs CMV infection reactivation: [redacted]% and CMV infection: [redacted]%). Similarly, most frequent Grade ≥3 AEs suspected to be related to ruxolitinib were those of cytopenia, including thrombocytopenia ([redacted]%), anaemia ([redacted]%), platelet count decreased ([redacted]%), neutropenia ([redacted]%), WBC count decreased ([redacted]%), neutrophil count decreased ([redacted]%) and leukopenia ([redacted]%). In the BAT arm, the most frequent AEs by PT (all grades) suspected to be related to study treatment (in ≥5% of patients) were CMV infection (combined for PTs CMV infection reactivation: [redacted]% and CMV infection: [redacted]%), followed by those of cytopenia, including WBC count decreased ([redacted]%), anaemia ([redacted]%) and platelet count decreased ([redacted]%). Grade ≥3 AEs suspected to be related to study treatment in the BAT arm were primarily cytopenia PTs, including WBC decreased ([redacted]%) and platelet count decreased ([redacted]%).

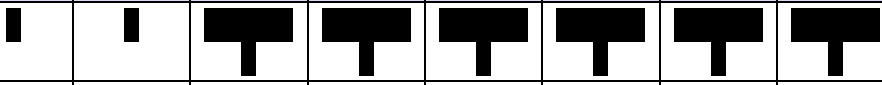
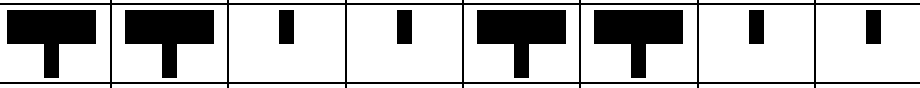
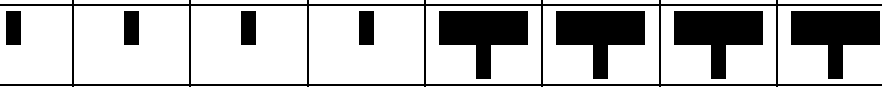
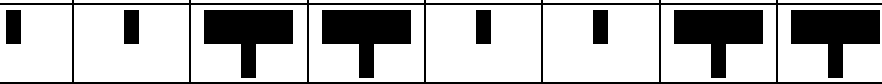
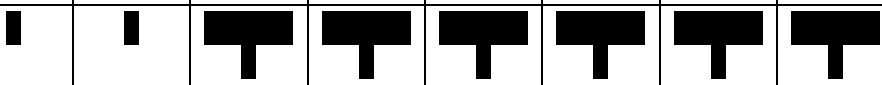
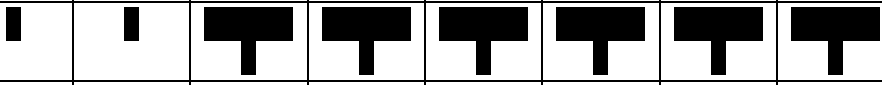
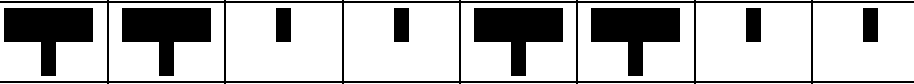
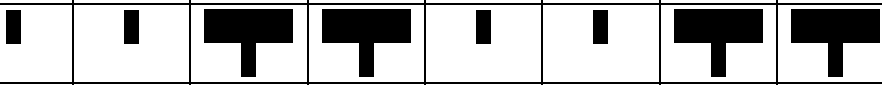
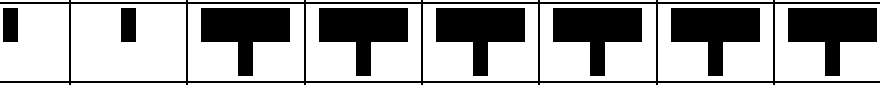
3.2.5.1.3 Serious adverse events

Up to Day 28, a similar proportion of patients in the ruxolitinib arm ([redacted]%) and in the BAT arm ([redacted]%) experienced an SAE. The incidence of Grade ≥3 SAEs was [redacted]% in the ruxolitinib arm and [redacted]% in the BAT arm. In the ruxolitinib arm, sepsis ([redacted]%) was the only Grade ≥3 SAE by PT observed in >5% of patients. In the BAT arm, CMV infection reactivation ([redacted]%), septic shock ([redacted]%) and respiratory failure (2.7%) were the most frequent Grade ≥3 SAE by PT.

During the randomised treatment period, SAEs were observed in [redacted]% of patients in the ruxolitinib arm and [redacted]% in the BAT arm. The proportion of patients with Grade ≥3 SAEs was higher in the ruxolitinib arm ([redacted]%) than the BAT arm ([redacted]%). In the ruxolitinib arm, sepsis ([redacted]%), septic shock ([redacted]%) and diarrhoea ([redacted]%) were the only Grade ≥3 SAEs by PT observed in ≥5% of patients. In the BAT arm, sepsis ([redacted]%), septic shock ([redacted]%), pneumonia ([redacted]%) and CMV infection (combined for PTs CMV infection reactivation: [redacted]% and CMV infection: [redacted]%) were the only Grade ≥3 SAEs by PT occurring in ≥5% of patients.

Table 3.15: Serious AEs by PT, occurring in ≥2% of patients in either arm, in either time period – REACH2, final analysis, safety set

	Up to Day 28				Randomised treatment period			
	Ruxolitinib N=152		BAT N=150		Ruxolitinib N=152		BAT N=150	
	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
Number of patients with at least one event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute respiratory failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Up to Day 28				Randomised treatment period			
	Ruxolitinib N=152		BAT N=150		Ruxolitinib N=152		BAT N=150	
	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
Bacteraemia								
Blood bilirubin increased								
CMV colitis								
CMV infection								
CMV infection reactivation								
Confusional state								
Diarrhoea								
Febrile neutropenia								
GvHD								
Multiple organ dysfunction syndrome								
Neutropenia								
Pancytopenia								
Platelet count decreased								
Pneumonia								
Pseudomonal sepsis								
Pyrexia								
Renal failure								
Respiratory failure								
Sepsis								

	Up to Day 28				Randomised treatment period			
	Ruxolitinib N=152		BAT N=150		Ruxolitinib N=152		BAT N=150	
	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
Septic shock	[redacted]							

Based on Table 17 of CS[3]
AE = adverse event; BAT = best available therapy; CS = company submission; CMV = cytomegalovirus; GvHD = graft-versus-host disease; PT = preferred term

3.2.5.1.4 Deaths

During the randomised treatment period, a similar proportion of patients died in the ruxolitinib arm (58.6%) and in the BAT arm (59.3%). Deaths due to aGvHD (including aGvHD and/or complications attributed to treatment for aGvHD) occurred in 25% of patients in the ruxolitinib arm and 25.3% of patients in the BAT arm. In the ruxolitinib arm, the other frequent causes of death were sepsis and multiple organ dysfunction syndrome (3.3% each), underlying haematological disease progression (2.6%) and septic shock (2.0%). In the BAT arm, the other frequent causes of death were: sepsis (3.3%), respiratory failure (2.7%), multiple organ dysfunction syndrome, septic shock and acute myeloid leukaemia (AML) recurrent (2.0% each).

On treatment death

On-randomised treatment deaths were defined as deaths from date of first administration of randomised treatment to 30 days after the last administration of randomised treatment. Up to Day 28, there were fewer on-treatment deaths in the ruxolitinib arm (9.9%) than in the BAT arm (14.0%). Up to the final database lock, on-treatment deaths occurred in 28.3% and 24.0% of patients in the ruxolitinib and in the BAT arms, respectively. The most common cause of death was the study indication (including aGvHD and/or complications attributed to treatment for aGvHD) in both the ruxolitinib (13.8%) and the BAT arms (14.0%).

Serious adverse events with fatal outcomes

Up to Day 28, the proportions of patients with SAEs with fatal outcome were similar between the two treatment arms (7.9% in the ruxolitinib arm and 11.3% in the BAT arm). A total of 3.9% of patients in the ruxolitinib arm and 8.7% of patients in the BAT arm had fatal SAEs due to the study indication. The majority of the fatal SAEs up to Day 28 were not suspected to be related to study treatment. During the randomised treatment period, SAEs with fatal outcome occurred in similar proportions of patients in both treatment arms (ruxolitinib arm: 21.7%; BAT arm: 21.3%). Sepsis (5.3%) and septic shock (4.6%) were the most common SAEs with a fatal outcome in the ruxolitinib arm (≥2%). The most common SAEs with a fatal outcome in the BAT arm (≥2%) were: sepsis, septic shock, respiratory failure, pneumonia (2.7% each) and multiple organ dysfunction syndrome, GvHD (2.0% each).

EAG comment: The company was asked to present a summary of AEs for the randomised treatment period separately by each type of BAT (including ECP separately). This summary should include the following: serious AEs, any fatal AE, and any grade 3+ AE, and any AE leading to discontinuation, presented as in Table 17 of the CS with both follow-up time points. The company response that *"As stated in question A7 d) i), the comparator in the final scope and DP is ECM without ruxolitinib, which*

is equivalent to BAT (a basket of therapies). This was further validated with UK clinical experts. The CS therefore looks at BAT, and we consider that it is not warranted to separate and analyse each of the individual treatments as suggested in this question. Please see Section B.2.10.1 in the CS for a summary and further detail relating to BAT adverse events." Lack of separate details of each type of BAT AEs is therefore part of the key issue regarding comparison with specific ECM treatments including ECP.

3.2.5.2 REACH1

3.2.5.2.1 Overview of adverse events

The median duration of ruxolitinib treatment was 46.0 days (range: 4–811 days), and the median average reported daily dose was 10.21 mg/day (range: 5.1–19.7 mg/day) (2). On Day 1, 97.2% of patients were receiving ruxolitinib 5 mg twice daily (BID), and 2.8% of patients were receiving ruxolitinib 5 mg once daily (QD). By Day 7, more than half of the patients (52.2%) who were still receiving ruxolitinib had their ruxolitinib dose increased to 10 mg BID.

In the safety evaluable population (N=71), all patients (100%) had at least one AE, [redacted] had at least one AE assessed by the investigator as related to ruxolitinib treatment, 39.4% had at least one fatal AE, 83.1% had at least one SAE and 32.4% had at least one AE leading to discontinuation of ruxolitinib treatment.

The most frequently reported AEs were erythropenia (64.8%; PT of anaemia), thrombocytopenia (62.0%; PTs of thrombocytopenia and platelet count decreased), and neutropenia (49.3%; PTs of neutropenia, febrile neutropenia, and neutrophil count decreased), consistent with the mechanism of action of ruxolitinib as well as the disease under study.

The most frequently reported treatment-related AEs were thrombocytopenia ([redacted]%), erythropenia ([redacted]%), neutropenia ([redacted]%), WBC count decreased ([redacted]%), alanine aminotransferase (ALT) increased ([redacted]%), and lymphocyte count decreased ([redacted]%). These events were also consistent with the disease under study, concomitant illnesses (e.g. CMV or other viral infection), and/or known effects of other concomitant medications (e.g., ganciclovir, valganciclovir).

The most frequently reported SAEs were sepsis (12.7%), pyrexia (11.3%), respiratory failure (9.9%), lung infection (7.0%) and pneumonia (7.0%). The majority of other serious SAEs occurred in [redacted]% of patients each.

The Medical Dictionary for Regulatory Activities (MedDRA) system organ classes (SOC) with the highest numbers of fatal AEs were infections and infestations (14.1%) and respiratory, thoracic, and mediastinal disorders (9.9%). The most frequently reported fatal AE was respiratory failure (8.5% of patients). No fatal AEs were attributed to ruxolitinib alone. Fatal AEs (pulmonary haemorrhage and sepsis) that were considered by the investigator to be related to both ruxolitinib and corticosteroid treatment occurred in 2.8% of patients. Fatal AEs (including sepsis, septic shock, device-related infection, multiple organ dysfunction syndrome, respiratory failure, candida infection, pneumonia legionella, staphylococcal bacteraemia, and pulmonary haemorrhage) that were considered to be related to corticosteroid use occurred in 11.3% of patients.

Adverse events leading to discontinuation of ruxolitinib treatment by PT for more than one patient were sepsis (5.6%), thrombocytopenia (2.8%), acute kidney injury (2.8%), and respiratory failure (2.8%).

3.2.6 REACH3

EAG comment: REACH3 was omitted from the clinical effectiveness Section of the original CS. The EAG agreed that the focus of the submission is on patients with aGvHD who have an inadequate response to corticosteroids. However, due to several parameters in the cost effectiveness analysis (CEA) being estimated from the data of REACH3, the company was asked to provide a full description of REACH3, including baseline characteristics and all outcomes.[6]

3.2.6.1 Baseline characteristics

In the company response to clarification,[5] the company provided the following Table 3.16 for patient baseline characteristics.

Table 3.16: Demographics and baseline characteristics – REACH3, Full analysis set

Demographic variable	RUX N=165	BAT N=164	All Patients N=329
Age (years)			
n	165	164	329
Mean (SD)	45.9 (15.68)	47.2 (16.17)	46.5 (15.92)
Median	49.0	50.0	49.0
Q1–Q3	[redacted]	[redacted]	[redacted]
Min – Max	13.0–73.0	12.0–76.0	12.0–76.0
Age category – n (%)			
Adolescents, 12 – <18 years	4 (2.4)	8 (4.9)	12 (3.6)
18 – 65 years	143 (86.7)	134 (81.7)	277 (84.2)
>65 years	18 (10.9)	22 (13.4)	40 (12.2)
Sex –n (%)			
Female	56 (33.9)	72 (43.9)	128 (38.9)
Male	109 (66.1)	92 (56.1)	201 (61.1)
Race –n (%)			
White	116 (70.3)	132 (80.5)	248 (75.4)
Black or African American	2 (1.2)	0	2 (0.6)
Asian	33 (20.0)	21 (12.8)	54 (16.4)
American Indian or Alaska Native	2 (1.2)	0	2 (0.6)
Other	9 (5.5)	4 (2.4)	13 (4.0)
Unknown	3 (1.8)	7 (4.3)	10 (3.0)
Ethnicity –n (%)			
Hispanic/Latino	[redacted]	[redacted]	[redacted]
Not Hispanic/Latino	[redacted]	[redacted]	[redacted]
Not Reported	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Weight (kg)			
n	165	163	328
Mean (SD)	68.5 (18.29)	67.9 (16.71)	68.2 (17.50)
Median	[redacted]	[redacted]	[redacted]
Q1–Q3	[redacted]	[redacted]	[redacted]

Demographic variable	RUX N=165	BAT N=164	All Patients N=329
Min – Max	32.0–128.0	37.0–128.5	32.0–128.5
Height (cm)			
n	143	150	293
Mean (SD)	169.7 (9.77)	169.4 (10.05)	169.6 (9.90)
Median	[redacted]	[redacted]	[redacted]
Q1–Q3	[redacted]	[redacted]	[redacted]
Min – Max	145.0–191.0	144.3–196.0	144.3–196.0
Body mass index (kg/m^2)			
n	143	150	293
Mean (SD)	23.4 (5.35)	23.5 (4.92)	23.4 (5.13)
Median	[redacted]	[redacted]	[redacted]
Q1–Q3	[redacted]	[redacted]	[redacted]
Min – Max	13.0–38.7	14.7–42.9	13.0–42.9
Assessment of performance status – n (%)			
ECOG	[redacted]	[redacted]	[redacted]
Karnofsky	[redacted]	[redacted]	[redacted]
Lansky	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
ECOG performance status – n (%)			
0	39 (23.6)	42 (25.6)	81 (24.6)
1	92 (55.8)	82 (50.0)	174 (52.9)
2	22 (13.3)	22 (13.4)	44 (13.4)
3	0	2 (1.2)	2 (0.6)
Missing	12 (7.3)	16 (9.8)	28 (8.5)
Karnofsky performance status – n (%)			
≥ 90	[redacted]	[redacted]	[redacted]
70 – 80	[redacted]	[redacted]	[redacted]
50 – 60	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Lansky performance status – n (%)			
≥ 90	[redacted]	[redacted]	[redacted]
70 – 80	[redacted]	[redacted]	[redacted]
50 – 60	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]

Based on Table 1 of response to clarification[5] [redacted] BAT = best available therapy; ECOG = Eastern Cooperative Oncology Group; FAS = full analysis set; min = minimum; max = maximum; NR = not reported; Q = quartile; SD = standard deviation

3.2.6.2 Efficacy results of REACH3

The company provided a summary of the full efficacy results of the primary and key secondary endpoints for REACH3 from the response to clarification.[5] Please find it as below.

- "*The study met the primary and both key secondary objectives showing superiority of ruxolitinib compared with BAT for ORR, FFS, and modified Lee Symptom Scale (mLSS): response of the total symptom score (TSS) of the mLSS (at Cycle 7 Day 1)*

- *The superiority of ORR in the ruxolitinib arm was established in the interim analysis (ORR: [redacted]% [95%CI: [redacted]] in the ruxolitinib arm and 26.3% [95%CI: 17.9, 36.1] in the BAT arm; p=0.0003) and maintained in the primary analysis (ORR: 49.7% [95%CI: 41.8, 57.6] in the ruxolitinib arm and 25.6% [95%CI: 19.1, 33.0] in the BAT arm; p<0.0001)*
- *After crossover treatment period, ORR at Cycle 7 Day 1 for ruxolitinib was 50.0% (95% CI: 37.8, 62.2) and similar in line with the ORR observed at Cycle 7 Day 1 during primary analysis and interim analysis*
- *Final analysis of FFS based on data collected from 329 subjects showed the 3-month and 6-month FFS probability was [redacted]% (95% CI: [redacted]) and [redacted]% (95% CI: [redacted]) for ruxolitinib and [redacted]% (95% CI: [redacted]) and [redacted]% (95% CI: [redacted]) for BAT, respectively*
- *The rate of responders based on the mLSS (as per improvement ≥ 7 points of TSS from baseline) showed a statistically significant difference between the treatment arms with p=0.0011. The odds ratio was 2.62 (95% CI: 1.42; 4.82). The response rate was 24.2% (95% CI: 17.9, 31.5) in the ruxolitinib group and 11.0% (95% CI: 6.6, 16.8) in the BAT arm.*"[5]

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Not applicable.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

Not applicable.

3.5 Additional work on clinical effectiveness undertaken by the EAG

Not applicable.

3.6 Conclusions of the clinical effectiveness section

The CS[3] and response to clarification[5] provided sufficient details for the EAG to appraise the literature searches conducted to identify relevant clinical evidence on the efficacy and safety of ruxolitinib and relevant comparators for the treatment of patients with steroid-refractory aGvHD or cGvHD aged ≥12 years. Searches were conducted in November 2019, with updates in September 2021 and January 2024. Searches were transparent and reproducible, and comprehensive strategies were used. Bibliographic databases, HTA Agency websites, conference proceedings and trials registers were searched. Overall, the EAG has no major concerns about the literature searches conducted.

The clinical effectiveness systematic review revealed two trials of the intervention, the key one being REACH2, which is an RCT comparing ruxolitinib to BAT, the other being REACH1, which is a single arm trial. In REACH2, for the primary outcome, i.e. ORR, there was a statistically significant difference in favour of ruxolitinib (stratified Cochrane-Mantel-Haenszel (CMH) test p<0.0001, one-sided, odds ratio: 2.64 with 95% confidence interval [CI]: 1.65, 4.22). Failure-free survival with ruxolitinib was also statistically significantly longer than with BAT (4.86 months versus 1.02 months; HR: 0.51, 95% CI: 0.39, 0.66; p<0.0001). There was also a 15% reduction in the risk of death in the ruxolitinib arm relative to the BAT arm (HR: 0.85; 95% CI: 0.63, 1.14), although not statistically significant. However,

the cumulative incidence of cGvHD was [redacted] for ruxolitinib at all time points (6, 12, 18, 24 months: [redacted] versus [redacted], [redacted]% versus [redacted]%, [redacted]% versus [redacted]% and [redacted]% versus [redacted]%, respectively).

As already mentioned in Section 2, one of the main limitations of REACH2 is that there were no Grade I patients and only 3% of patients in REACH2 were adolescents, which limits applicability to these patients in UK clinical practice. This is therefore a key issue.

Another limitation, in terms of providing evidence to compare ruxolitinib to any appropriate comparator, is in BAT being a mixture of treatments and that only 27.3% received ECP, which is what appears to be the most common form of ECM in the UK. As already mentioned in Section 2, it could be that there are subgroups each with a different comparator, including one for those eligible for ECP. However, the company refused to conduct such an analysis partly on the basis of clinical expert opinion that BAT in the trial reflected UK clinical practice, partly on the basis of clinical expert opinion that efficacy would change little with specific BAT treatment and partly on the basis of the RCT, which was not stratified by such subgroups or specific investigator choice. However, the company had already provided in the cost effectiveness Section a small amount of evidence by specific BAT treatment, a set of K-M plots for FFS, but without any summary statistics, to which they add a similar plot for OS in the response to the clarification letter. They claimed that this showed little variation. However, the EAG consider that it appears to show that ECP is at least one of the most effective treatments and that the others were given to very few patients in the REACH2 trial. Therefore, it is plausible that, if more patients had received ECP then the efficacy of BAT might have been greater. Given that both of the EAG clinical experts consider that ECP should be offered to most patients, this is therefore a key issue.

Another significant limitation is that crossover was permitted from BAT to ruxolitinib, which occurred in n=49 out of 155 patients. A crossover adjustment result shown a [redacted] in the rate of death in the ruxolitinib arm relative to the BAT arm (HR: [redacted]; 95% CI: [redacted]) while the unadjusted result shown a 15% reduction in the rate of death with HR of 0.85 (95% CI: 0.63, 1.14). However, given that death would preclude progression to cGvHD it seems likely that crossover also inflated the incidence of cGvHD, which means that ruxolitinib might have a worse effect in comparison to ECM in clinical practice than observed in the trial. This is, of course, made more uncertain by any mismatch between BAT and ECM. This is therefore a key issue.

It is also worth noting that, although REACH2 is the key trial, being an RCT, REACH1 did show poorer survival outcomes: for median FFS, 2.80 months versus 4.86 months and, for median OS, 7.63 versus 10.71 months. There is no clear explanation for this, which indicates that it is a key issue.

The company stated that across REACH2 and REACH1, ruxolitinib was generally well-tolerated in patients with SR-aGvHD, and that there were no unexpected toxicities observed with ruxolitinib. However, in REACH2, over the randomised treatment period, there were more treatment-related, SAEs, and AEs leading to discontinuation with ruxolitinib, although rate of fatal AEs was similar.

4. Cost effectiveness

4.1 EAG comment on company's review of cost effectiveness evidence

This Section pertains mainly to the review of CEA studies. However, the search Section (4.1.1) also contains summaries and critiques of other searches related to cost effectiveness presented in the CS. Therefore, the following Section includes searches for the CEA review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

4.1.1 Searches performed for cost effectiveness section

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness, HRQoL and cost/resource use identification presented in the CS.[3] The CADTH evidence-based checklist for the PRESS, was used to inform this critique.[9] The EAG has presented only the major limitations of each search strategy in the report.

Appendices G, H and I of the CS provide details of an SLR conducted to identify relevant studies on cost effectiveness, HRQoL and cost and resource use in patients with aGvHD or cGvHD.[15-17] The searches were conducted in July 2019, with updates in September 2021 and January 2024. A summary of the sources searched is provided in Table 4.1.

Table 4.1: Data sources searched for economic evaluations, HRQoL and cost/health care resource use (as reported in CS)

Resource	Host/Source	Date Ranges	Date searched
Electronic databases			
Embase	Ovid	1974-31.7.19 Jul 2019-9.9.21 10.9.21-10.1.24	31.7.19 10.9.21 11.1.24
MEDLINE	Ovid	1946-31.7.19 Jul 2019-9.9.21 10.9.21-10.1.24	31.7.19 10.9.21 11.1.24
CENTRAL	Ovid	Inception-June 2019 July 2019-Aug 2021 2021-Dec 2023	31.7.19 10.9.21 11.1.24
NHS EED	Ovid	Incep-1st quarter 2016	31.7.19 10.9.21 11.1.24
HTAD	Ovid	Incep-4th quarter 2016	11.1.24
Additional resources			
CEA Registry RePeC EQ-5D Publications Database International HTA Database	Internet	No date limits	Feb 2024

Resource	Host/Source	Date Ranges	Date searched
HTA Agencies			
NICE NCPE SMC HAS IQWiG G-BA SBU CADTH PBAC ICER	Internet	No date limits	Feb 2024
Conferences			
ASH annual conference EHA annual meeting EBMT annual meeting Tandem meetings: ASTCT/ ICBMRT BOPA ISPOR ISPOR Europe	Internet	2021-2023 2021-2023 2021-2023 2021-2024 2021-2023 2021-2023 2021-2023	Mar 2024
Trials registries			
ClinicalTrials.gov WHO ICTRP	Internet	No date limits	11.3.24

ASH = American Society of Haematology; ASTCT = Transplantation & Cellular Therapy Meetings of the American Society for Transplantation and Cellular Therapy; BOPA = British Oncology Pharmacy Association; CADTH = Canadian Agency for Drugs and Technologies in Health; CEA Registry = Cost Effectiveness Analysis Registry; CENTRAL = Cochrane Central Register of Controlled Trials; CIBMTR = Center for International Blood and Marrow Transplant Research; CS = company submission; EBMT = European Bone Marrow Transplant; EHA = European Hematology Association; G-BA = Gemeinsamer Bundesausschuss; HAS = Haute Autorité de Santé; HRQoL = health-related quality of life; HTAD = HTA Database; ICER = Institute for Clinical and Economic Review; IQWiG = German Institute for Quality and Efficiency in Health Care; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; NCPE = National Centre for Pharmacoeconomics; NHS EED = NHS Economic Evaluation Database; PBAC = Pharmaceutical Benefits Advisory Committee; RePeC = Research Papers in Economics; SBU = Swedish Agency for Health Technology Assessment and Assessment of Social Services; SMC = Scottish Medicines Consortium; WHO ICTRP = World Health Organization International Clinical Trials Registry Platform

EAG comment:

- A single set of searches was undertaken to identify relevant studies on cost effectiveness and cost/health care resource use in patients with aGvHD or cGvHD aged ≥12 years. A separate set of searches was conducted to identify HRQoL and health state utility value (HSUV) data in the same population. The CS, Appendix G, H, and the company's response to clarification provided sufficient details for the EAG to appraise the literature searches.[3, 5, 15, 16]
- An extensive range of bibliographic database searches, HTA organisation websites, grey literature resources and conferences proceedings were searched. In addition to the resources listed in the table above, over 50 additional websites were handsearched. Reference checking was conducted.
- Searches were extremely well structured, transparent and reproducible, and made good use of free text, subject indexing terms and the available database syntax.

- The database searches contained a facet for GvHD. In the Embase, MEDLINE and CENTRAL searches, this was then combined with study design filters for economic evaluations/cost studies in the economic evaluation/health care resource utilisation (HCRU) SLR, and a filter for utilities/quality of life (QoL) studies in the HRQoL SLR. The study design filters used were not referenced, however all contained an extensive combination of subject heading terms and free text terms, and the EAG considered them appropriate.
- Animal-only studies were excluded where possible.
- No date or language limits were applied to the searches.
- As with the clinical effectiveness searches (Section 3.1.1), search terms were included which attempted to exclude paediatric studies. Although this was done with caution, there is still the potential for this approach to risk omitting potentially relevant studies due to inaccuracies in database indexing. However, the EAG believes that the extensive searches conducted on multiple resources may have mitigated against this limitation in the search strategy.
- None of the study design filters used were referenced, however all contained an extensive combination of subject heading terms and free text terms, and the EAG considered them appropriate.

4.1.2 Inclusion/exclusion criteria

The in- and exclusion criteria used by the company for cost effectiveness and cost and resource use studies are presented in Appendix G, Table 7 (search date July 2019, updates in September 2021 and January 2024), and for HRQoL and HSUV studies in appendix H, Table 8.[15, 16] The EAG considers the in- and exclusion criteria to a large extent suitable to capture all relevant evidence, though some relevant papers may have been missed due to exclusion of papers based on language.

4.1.3 Findings of the cost-effectiveness review

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram for the QoL and HSUV studies is presented in Figure 1, 2 and 3 of Appendix H and in Figure 1, 2 and 3 of Appendix G for cost effectiveness and cost and resource use studies and includes studies for both acute and chronic GVHD.[15, 16] Studies on cGvHD only were not presented. The PRISMA diagram for QoL and HSUV studies indicate that 34 records were included from the SLR across the de novo SLR and two subsequent updates. Nineteen studies were relevant to the decision problem and 15 studies on cGvHD only were included but not presented. A summary list is provided in Table 10 of Appendix H.[16] The PRISMA diagrams for cost effectiveness and cost and resource use studies indicate that 106 records were included from the SLR across the de novo SLR and two subsequent updates. Fifty-four studies were relevant to the decision problem and 49 studies on cGvHD only were included but not presented. Of the 54 relevant publications, four related to four unique economic evaluations (though none in the UK) and 50 related to 42 unique HCRU and/or cost studies. Further details of the HCRU and cost studies are presented in Appendix I. A summary list is provided in Table 9 of Appendix G.[15]

Overall, the CS,[3] and response to clarification[5] provided sufficient details for the EAG to appraise the literature searches conducted to identify relevant clinical evidence on cost effectiveness, HRQoL and cost/health care resource use in patients with aGvHD or cGvHD. Searches were conducted in July 2019, with updates in September 2021 and January 2024. Searches were transparent and reproducible, and comprehensive strategies were used. Bibliographic databases, HTA Agency websites, conference proceedings and trials registers were searched. Overall, the EAG has no major concerns about the literature searches conducted.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 4.2: NICE reference case checklist

Element of HTA	Reference case	EAG comment on CS
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	As per the reference case
Perspective on costs	NHS and PSS	As per the reference case
Type of economic evaluation	Cost utility analysis with fully incremental analysis	As per the reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	As per the reference case
Synthesis of evidence on health effects	Based on systematic review	Evidence was used from the REACH2 (acute GvHD) and REACH3 (chronic GvHD) clinical studies
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	As per the reference case
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	As per the reference case
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	As per the reference case
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	As per the reference case. A potential equity issue is raised by the company in the CS where it is mentioned that ECP availability is limited to five therapeutic apheresis services units in England and that travel time increases the risk of infections. The eligibility for ECP also depends on patients having a good venous access and being haematologically stable. Currently, some centres in England use their own budget to enable patient access to ruxolitinib. Some patients self-fund or use private healthcare to access ruxolitinib, which creates inequity in patients

Element of HTA	Reference case	EAG comment on CS
		with GvHD across England. In Wales and Scotland, patients already have access to ruxolitinib, which creates inequity of access across the UK
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	As per the reference case
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	As per the reference case
CS = company submission; EAG = Evidence Assessment Group; ECP = extracorporeal photopheresis; EQ-5D = EuroQoL-5 Dimensions; GvHD = graft-versus-host disease; HRQoL= health-related quality of life; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; HTA = Health Technology Assessment; PSS = Personal Social Services; QALY = quality-adjusted life year; UK = United Kingdom		

4.2.2 Model structure

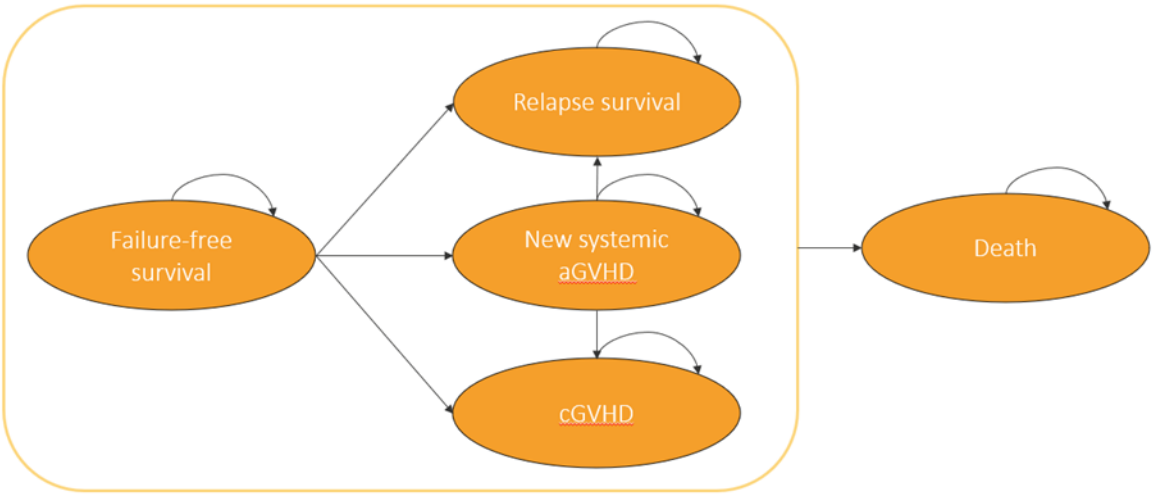
The company developed a cost-effectiveness model in Microsoft Excel® to assess the cost effectiveness of ruxolitinib compared to BAT for treating patients with aGvHD aged 12 years and older who have an inadequate response to corticosteroids.

The model adopts a multi-state model (MSM) approach, as patients can transition through several mutually exclusive health states via estimated transition probabilities. The company chose to use an MSM approach over a partitioned survival model as this could account for differences in costs and quality-adjusted life-years (QALY) of patients experiencing the clinically distinct events that make up the failure-free survival data that were available in the clinical trials of ruxolitinib. According to the company, this approach also aligns with the EAG's suggestions on the NICE appraisal of belumosudil in cGvHD patients (TA949) and is assumed to better reflect the natural history of the condition.[18] Therefore, the model was structured using the following seven mutually exclusive health states, where patients can only occupy one state at the time and death being an absorbing state:

- Failure-free (FF)
- New systemic treatment (NST)
- Disease relapse
- cGvHD FF
- cGvHD requiring NST
- Relapse following cGvHD
- Death

Figure 4.1 shows the model structure. Note that the cGvHD health state presented below consists of three different sub-health states (cGvHD FF, cGvHD NST and cGvHD relapse), as mentioned above.

Figure 4.1: Model structure



Based on Figure 7 of the CS[3]
aGvHD = acute graft-versus-host disease; cGvHD = chronic graft-versus-host disease; CS = company submission

Steroid-refractory acute patients (aGvHD) were assumed to enter the model in the FF health state and receive either ruxolitinib or BAT. The proportion of patients in FF was determined by the FFS curves derived from the REACH2 trial. Patients were assumed to stay in this health state until they experience a *treatment failure* as defined in REACH2, where patients then would receive a new systemic therapy for aGvHD, experience a relapse of their underlying malignancy, or experience NRM. In addition, patients in the aGvHD FF health state can also transition to the cGvHD FF health state if they develop chronic GvHD. The CS stated that '*within the assessment of FFS, the development of cGvHD was treated as a competing risk'*.[3] In response to Clarification Question A10c,[5] the company explained that this is because in the CSR analyses, the event of cGvHD was not considered as a censoring event. Therefore, the cumulative incidence function was estimated. However, in the economic analysis, any competing events are treated as censoring events when estimating the transition probabilities for multiple event outcomes. Acute GvHD patients entering the NST health state receive a BAT and are assumed to stay in this health state until they experience a relapse of their underlying malignancy, develop cGvHD, or die. Relapsed patients were assumed to either stay in this health state or die (clarification response B1g).[5]

Similar to the aGvHD FF health state, patients entering the cGvHD health state were assumed to remain failure-free until they experience *treatment failure* as defined in the REACH3 trial, where patients would then receive a new systemic cGvHD therapy, experience a relapse of their underlying malignancy, or die (without relapsing). Patients entering the cGvHD NST state were assumed to receive a third-line cGvHD treatment (i.e., another BAT but with different frequency compared to second line) and stay in this state until they relapse or die. Relapsed patients with cGvHD disease can either stay in this health state or die.

Costs and utilities were applied to each health state to calculate total costs and QALYs per model cycle, which was set at 28 days (4 weeks). A half-cycle correction was implemented to account for events happening at any time during the cycle. The input values of the model and their underlying assumptions are further elaborated in the remaining of Section 4 of the EAG report.

EAG comment: The main concern of the EAG is that since response to treatment is not implicitly included in the model, it seems that the FF health state includes a mixture of patients who are still experiencing aGvHD symptoms and those that are in remission after treatment response. In that sense:

a) The model cannot distinguish between these two subgroups of patients who are likely to experience very different survival and QoL outcomes.
b) It seems likely that this mixture changes over time, as those who continue to experience aGvHD symptoms will probably transition to another treatment (NST). This might explain why the utilities observed in REACH2 increase during the first 20 weeks (see Table 4.7 in Section 4.2.8). This might be interpreted as an attempt to account for those patients achieving remission after treatment response, but it is uncertain.
c) This distinction is expected to be relevant for patients who transition from FF aGvHD to another health state. For example, patients in FF transitioning to cGvHD (FF) for whom their aGvHD symptoms are not yet resolved would presumably have worse survival and QoL outcomes than those in FF in remission after treatment response transitioning to cGvHD.

4.2.3 Population

Consistent with the NICE scope, the population considered in the CS was patients with aGvHD aged 12 years and older who have an inadequate response to corticosteroids. The patient population aligns with the anticipated licensed indication of ruxolitinib and is consistent with the patient population included in the REACH2 trial (see Section 3.2.1).[19]

The key baseline patient characteristics in the economic model are listed in Table 4.3. Patients included in the economic model were assumed to have an average baseline age of 49.5 years, a mean weight of 66.87 kg, a mean body surface area of 1.77 m^2, and consist of a 59% male population based on the REACH2 trial population characteristics.

Table 4.3: Key baseline patient characteristics used in the economic model

Parameter	Mean	SD	Source
Mean age (years)	49.5	15.69	REACH2[19]
Proportion female (%)	41%	–	
Mean weight (kg)	66.87	14.41	
BSA (m^2)	1.77	0.22	
Based on Table 22 of the CS[3] BSA = body surface area; CS = company submission; kg = kilogram; m^2 = square metre; SD = standard deviation			

EAG comment: As mentioned in Section 2.1, there is lack of evidence of similarity of treatment effect for both adolescents and Grade I disease. These concerns are also relevant for the CEA since it is uncertain whether the analyses results can be generalised to these subgroups of patients.

Furthermore, the EAG considers that there are many uncertainties when it comes to the modelling of patients in the chronic health state (cGvHD). These are summarised below:

a) In response to Clarification Question B1(a), the company stated that "*the cGvHD population that is included in the economic model is patients who first had aGvHD and developed cGvHD before or after the symptoms of aGvHD were resolved*".[5] However, the economic model uses data from REACH3 to model (survival and QoL) outcomes for patients developing cGvHD,

but the population in REACH3 "*includes patients with aGvHD prior to cGvHD and patients with de novo cGvHD*".[5] In particular, the company indicated that in REACH3, 88 of 164 patients (53.7%) in the BAT arm had prior aGvHD and 17 (10.4%) of these had SR-aGvHD, although it is also unclear whether for these patients the symptoms of aGvHD were resolved or not. The remaining 76 of 164 patients (46.3%) in the BAT arm had de novo cGvHD. It seems then that only 10.4% of patients in REACH3 are representative of the cGvHD patients being modelled. Based on this, the EAG considers that there seems to be a mismatch between the chronic population intended to be modelled and the population in REACH3.

b) Also, in response to Clarification Question B1(a), the company acknowledged some potential differences in population between *de novo* cGvHD patients and those in the economic model.[5] However, the company referred to the clinical experts they consulted who considered it reasonable to use the overall data from REACH3 as a proxy and that the outcomes in REACH3 are broadly reflective what they would expect in those developing cGvHD in the model.[20, 21] The EAG considers this still unclear since it seems to misalign with the definition of the patient population in REACH3 (only 10.4% of patients in REACH3 previously had steroid refractory aGvHD) and, furthermore, it seems to be unknown whether patients in REACH3, who previously had aGvHD, are in remission from the acute symptoms or not.

c) In Figure 3 of the response to Clarification Questions, the company presented a plot of FFS over time stratified by prior aGvHD in the BAT arm of REACH3.[5] The EAG agrees with the company that there is no apparent difference in FFS between the groups, however, we do not agree that this necessarily indicates that "*outcomes from REACH3 as a whole are generalisable to patients with prior aGvHD*".[5] Figure 3 shows FFS only, but other outcomes such as OS or QoL are also relevant to come up with such conclusion, and these are not presented. Furthermore, the stratification by prior aGvHD is informative, but it should be noted that the population modelled is SR-aGvHD; thus, a smaller subgroup, and even if it would result in very small sample, showing these results would be important. And as mentioned above, it is unclear if for patients in REACH3 acute symptoms were resolved or not. All these uncertainties are relevant in order to understand why patients in REACH3, and thus in the chronic part of the model, experience better (survival and QoL) outcomes than those in REACH2 (in the acute part of the model).

d) In response to Clarification Question B2a, the company explained that "*patients in the cGvHD state in the model may or may not have resolved aGvHD, and REACH3 enrolled patients with both interrupted and progressive disease*".[5] The clinical expert consulted by the EAG also noted that chronic patients that have aGvHD symptoms not resolved may be quite a different population than the chronic patients who have the acute disease resolved.[7] It is unclear to the EAG how many patients in the cGvHD of the model are assumed to develop a chronic disease without the aGvHD symptoms being resolved and if these patients would be expected to have very different clinical outcomes and QoL than chronic patients with the acute symptoms being resolved. The EAG clinical expert mentioned that patients with overlap GvHD, or those who rapidly develop severe cGvHD following aGvHD have a poorer prognosis at one year.[7]

e) Furthermore, one of the clinical experts consulted by the company also commented that patients with de novo cGvHD compared to patients who previously had aGvHD are very different as patients "*who have aGvHD and then develop cGvHD often have a higher degree of comorbidities with multiple infectious complications. They have worse performance status and are much sicker*".[20]

4.2.4 Interventions and comparators

The intervention considered in the CEAs was ruxolitinib, which is a self-administered oral treatment at a dosage of 10 mg twice per day as a continuous therapy, consistent with the licensed indication.[4] The CS stated that ruxolitinib can be administered at a maximum duration of around 2 years, as per the REACH2 trial protocol. Tapering of treatment could not start before Day 56 of the trial.[19]

In the cost effectiveness (CE) analyses, BAT was deemed to be the only relevant comparator in this submission. For details and EAG critique we refer to Section 2.3 of this report. Based on clinical experts feedback, the company concluded that BAT treatment options and their distributions in REACH2 trial did not fully represent UK clinical practice.[20, 21] In particular, ECP was under-represented in REACH2, whilst methotrexate and everolimus were not part of the BAT in the UK. Table 4.4 below shows a comparison between the BAT options in REACH2 (with their respective proportions) and those based on UK clinical expert input.[20, 21] Note that in REACH2, 3% of patients received no treatment, therefore the company re-weighted the proportions provided by the clinical experts to consider these patients in the economic analysis.

Table 4.4: BAT options in REACH2 and in UK clinical practice according to experts

Treatment	Proportion of REACH2 patients	Clinical expert input	Proportion used in the economic analysis
ATG	13%	0%	0%
ECP	27%	46%	45%
Etanercept	15%	15%	15%
Everolimus	1%	0%	0%
Infliximab	11%	15%	15%
Low-dose methotrexate	3%	0%	0%
MMF	17%	18%	17%
MSC	10%	5%	5%
Sirolimus	2%	1%	1%
No treatment	3%	–	3%

Based on Table 20 of the CS[3]
ATG = anti-thymocyte globulin; BAT = best available therapy; CS = company submission; ECP = extracorporeal photopheresis; MMF = mycophenolate mofetil; MSC = mesenchymal stromal cells; UK = United Kingdom

EAG comment: In Section 2.3, it is mentioned that the choice between ECP and the other treatments might be driven by clinical characteristics (such as haematological stability and venous access), implying that subgroup analysis should be used with the comparator varying by subgroup, with one being ECP. The cost effectiveness of these subgroups, if relevant, should be then analysed separately. Note that in the current version of the model it is possible to make changes to the proportion of patients receiving ECP, but this only affects the estimated total costs. In a subgroup analysis, patients characteristics and clinical effectiveness should match those in the subgroup. This, however, cannot be changed in the current model. If ECP alone is more effective than BAT, the incremental QALYs should decrease. But if life is also extended for ECP patients, which might be the case based on Figure 9 in the

clarification letter response (HR: 1.118, p=0.639),[5] the total costs of the ECP arm could increase as well. Therefore, it is uncertain if for this subgroup the ICER will increase or not.

4.2.5 Perspective, time horizon and discounting

The economic analysis is conducted from the NHS and PSS perspective. Discount rates of 3.5% are applied to both costs and benefits. The model cycle length is 28 days (four weeks) with a lifetime time horizon (50 years given the mean starting age of 49.50 years old in the model) and a half-cycle correction applied.

4.2.6 Treatment effectiveness and extrapolation

As discussed in Section 4.2.2, the model consists of seven mutually exclusive health states, from which patients may transition to another health state, or remain in the same health state, at each model cycle (four weeks). Table 4.5 presents an overview of all the possible transitions, and the data source that was used to estimate these transition probabilities, i.e., REACH 2 and REACH 3.[19, 22]

Table 4.5: Transition probabilities required for the model and data source used

To / From	Failure-free	NST	Relapse	cGvHD	cGvHD, NST	cGvHD, relapse	Death
Failure-free	#	R2	R2	R2	-	-	R2
NST	-	#	R2	R2	-	-	R2
Relapse	-	-	#	-	-	-	R2
cGvHD	-	-	-	#	R3	R3	R3
cGvHD, NST	-	-	-	-	#	R3	R3
cGvHD, relapse	-	-	-	-	-	#	R3
Death	-	-	-	-	-	-	1

Based on Table 23 CS[3]
# indicates that this probability is estimated as 1 minus the sum of other probabilities in the same row
- indicates that this transition is not possible
cGvHD = chronic graft-versus-host disease; CS = company submission; NST = new systemic therapy; R2 = REACH2; R3 = REACH3

For the three cGvHD health-states, the company used only the BAT arm of the REACH3 trial as ruxolitinib is not currently used in UK clinical practice in cGvHD. Additionally, UK clinical experts were asked what proportion of patients currently receive belumosudil in third line (3L) cGvHD. There was a consensus that around 35% of patients would receive belumosudil at 3L in cGvHD. In the model, this was reflected as an adjustment to costs only, because belumosudil does not have an impact on OS as per EAG critique in TA949.[18]

All transition probabilities were estimated according to the methods described for the implementation of state transitions models in NICE DSU TSD 19.[23] For each state, individual survival analyses were performed for each possible transition, treating any event which is not the event of interest as a

censoring event, i.e., "competing" events are treated in the same way as loss to follow-up. Each of the transitions is described by a time-to-event curve, and thus, the transition matrix is time dependent.

The company assumed that only the transition probabilities starting from the failure-free health-state would differ between treatments; for the transitions from NST and relapse, REACH2 data from the ruxolitinib and BAT groups were pooled for analysis.

As the model is specified for a lifetime horizon, the company had to extrapolate all time-to-event curves beyond the observation period in the REACH2 and REACH3 trials. Further details are presented in the next Section.

In REACH2, 49 patients in the BAT arm (32%) crossed over to ruxolitinib at the end of the randomised treatment period. In order to avoid biased estimates of post-failure outcomes the company applied crossover adjustment to OS, relapse-free survival and relapse and cGvHD-free survival, based on the two-stage method recommended in NICE DSU 16 to adjust survival times for crossover.[24] In all cases, the impact of crossover adjustment was minimal, with a maximum reduction on median survival of half a month. For details, please refer to Section 3.2 of this report.

4.2.6.1 Extrapolating survival curves

In the economic model, survival curves for ruxolitinib and BAT were estimated using FFS data from the REACH2 and REACH3 trials.[19, 22] Details about the clinical effectiveness reported in these trials can be found in Section 3.3 of this report. Survival curve fitting followed the NICE DSU guidelines.[23] The proportional hazard (PH) assumption was used to determine whether separate or joint models for each arm were preferable and was assessed using the log-log survival plots and global statistical test. Statistical goodness-of-fit measures (Akaike information criterion [AIC], Bayesian information criterion [BIC]), visual inspection, and clinical plausibility were used to choose the base-case survival curves. Various standard survival distributions were assessed including the exponential, generalised gamma, Gompertz, log-logistic, log-normal, and Weibull distributions.

4.2.6.1.1 Failure-free survival (aGvHD)

Figure 4.2 presents the KM data from REACH2 that were used to estimate the individual transitions from the FF health state for ruxolitinib and BAT. Compared to BAT, the main benefit of ruxolitinib treatment seems to be delaying the time to NST and, to a smaller extent, time to relapse.

Figure 4.2: Failure-free survival data from REACH2 for each of the individual transitions

Based on Figure 10 of the clarification letter response[5]
BAT = best available therapy; cGvHD = chronic graft-versus-host disease; NST = new systemic therapy

The PH assumption was evaluated for the comparison between ruxolitinib and BAT. The company indicated that the *global test* showed that the PH assumption upheld for all individual transitions from the FF aGvHD health state. The log-log plots also supported the PH for the transition from the failure-free to NST, while the curves crossed for the transitions to relapse and cGvHD health states and were nearly identical for the transition to death suggesting violation of PH for these transitions (Figure 18 of the CS).[3] To assess the plausibility of model extrapolations for the transitions from FF to NST, relapse and cGvHD, the company presented the KM data and fitted models for the BAT arm to clinicians, with the best (statistically) fitting models highlighted. In the Advisory Board Meeting it was mentioned that as OS is modelled indirectly in the CEM, a curve showing the KM from the trial and the modelled OS from the model were presented to ensure the clinical experts agree the OS prediction is close to what is observed in the trial.[21]

For the transition from FF to NST, the company concluded that joint models provided a good visual fit and clinically plausible long-term extrapolations. Therefore, in the base-case analysis a Gompertz model was used as per clinical experts' preferred model, whilst it also showed the best statistical fit. The company chose to also use joint models for the transition from FF to relapse and death, as separate individual models did not provide clinically plausible extrapolations due to the crossing of the ruxolitinib and BAT curves. It was noted that due to the censoring of competing events, it was not considered plausible to assume that the risk of failure or relapse would be higher with ruxolitinib compared with BAT. For both the transition from FF to relapse and to death, generalised gamma models were used in the company base-case grounded on the most preferred option of clinical experts and best statistically fitted model, respectively.

For the transition from FF to cGvHD, the company stated that independent models were selected irrespective of the crossing of the log-log curves to reflect the observed incidence of events within REACH2 after accounting for competing risks. Although the clinical experts preferred the Gompertz and gamma models as showing the slower failure over time, the company selected the generalised gamma as this had the best statistical fit. To address uncertainty due to parametric extrapolation, various scenario analyses which were considered clinically plausible were conducted.

EAG comment: The main concerns of the EAG regarding the extrapolation of the FFS data are summarised below:

a) The company indicated that '*model validation was undertaken using the individual models fit to the BAT data as the patterns of survival for BAT with each curve are comparable between the individual and joint models, and the choice of curves is not affected by the switch to joint models*'.[3] It is unclear what the company tried to achieve with this validation exercise, however, it should be noted that it seems that experts did not validate the predictions for the ruxolitinib arm. The EAG considers that it would have been better to show the ruxolitinib curves to the experts as well.
b) The low number of patients at risk after three months (as can be seen in Figure 4.2) suggests that there is high uncertainty associated to the survival data estimates and their long-term extrapolations. Therefore, results need to be assessed carefully.
c) The validity of crossing survival data (not only the extrapolations) is unclear.
    i. The company assumed joint models for the transitions from FF to relapse and death, since separate individual models would not provide clinically plausible extrapolations due to the crossing of the ruxolitinib and BAT curves. The EAG would like to note that this crossing is not only observed in the extrapolations but in the KM data as well. Therefore, if the validity of the extrapolations is questioned, the validity of the REACH2 data should also be questioned.
    ii. Likewise, the company indicated that due to the censoring of competing events, it was not considered plausible to assume that the risk of failure due to death or relapse would be higher with ruxolitinib compared with BAT, but again, this is what REACH2 data shows. For the transition from FF to relapse, the KM shows that both curves seem to converge and that there is no separation after 2 years. Assuming a PH model (see Figure 20 in CS) implies an immediate initial and continued benefit for ruxolitinib that does not appear to be supported by the observed data.
    iii. The company's estimation of the transition from FF to death seems incorrect since the KM curve for BAT is higher than the KM for ruxolitinib, but the opposite is seen in the extrapolated curves.
d) The selection of independent or PH extrapolation models is also problematic. The company refers to a global test to support PH models, but it is unclear what test is referred to. Based on Figure 4.2 and log-log plots in CS (Figure 18),[3] the EAG considers that the PH assumption is only plausible for time to NST. For other transitions, crossing curves and/or delayed separation is observed, which are not possible under PH.
e) For the transition from FF to cGvHD, the company stated that independent models were selected despite crossing log-log curves to reflect the observed incidence of events within REACH2 after accounting for competing risks. The EAG wonders why the same argument was not valid for FFS (acute) transitions where there is also crossing of survival curves (Figure 4.2).
    i. Regarding the selection of the preferred extrapolation curves, the company explained that clinical experts preferred the Gompertz and generalised gamma models, but the

company selected the generalised gamma based on the best statistical fit. As shown in Figure 20 of the CS,[3] the fit to the data seems to be poor in any case, meaning that there is uncertainty about the values used for these transitions in the model.

ii. In response to Clarification Question B1c,[5] the company contacted clinical experts who indicated that they did not expect the incidence of cGvHD to be different between BAT and ruxolitinib (after accounting for the competing events). Based on this, their base-case was updated and the same rate of cGvHD was assumed for both arms, which was estimated from the pooled ruxolitinib and BAT data in REACH2.

f) In general, the company's approach to survival data extrapolation seems to lack consistency, which in some cases results in implausible and/or contradictory decisions. A simple way to overcome some of these issues could be adopting a pragmatic approach where the only benefit of ruxolitinib over BAT would be on delaying time to NST. For the other transitions, acknowledging the outstanding uncertainties, these could be considered equal between both arms. This represents the EAG's preferred approach used to define the EAG base-case in Section 6 of this report.

4.2.6.1.2 Post-failure survival

Figure 4.3 presents the KM data from REACH2 that were used to estimate the individual transitions from the post-failure outcomes. The KM data in Figure 4.3 were adjusted for crossover. Differences between the ruxolitinib and BAT arms were deemed small for all transitions, which was confirmed by the lack of statistical significance found in the Cox proportional hazard models comparing the treatments. Therefore, the company used data from the pooled arms to estimate transitions for post-failure transitions.

For the transitions from NST to relapse and cGvHD, the company base-case employed exponential models. For the transition from NST to death and from relapse to death, a generalised gamma and a log-logistic model was used, respectively, justified based on best statistical fit criteria.

Figure 4.3: Post-failure survival data from REACH2 for each of the individual transitions

Based on Figure 11 of the clarification letter response[5]
BAT = best available therapy; cGvHD = chronic graft-versus-host disease; NST = new systemic therapy

EAG comments: The main concerns of the EAG are summarised below:

a) Figure 4.3 shows that the number of patients at risk used to estimate post-failure transitions is low compared to those in Figure 4.2, especially for ruxolitinib. This suggests that the estimated post-failure transitions are uncertain.
b) The company justified pooling ruxolitinib and BAT data to estimate transitions for post-failure based on small differences between arms for all transitions, which was confirmed by the lack of statistical significance found in the Cox proportional hazard models comparing the treatments. The company only reported p-values in Table 25 of the CS,[3] but the EAG would have preferred to see the complete outcome of the tests (i.e., hazard ratios and confidence intervals) since, as is well-known, p-values alone convey little information and can be misleading. In addition, it would have been of interest to see the results of Cox analyses for the (acute) FFS transitions as well, since some of the differences between arms in Figure 4.2 could be deemed as small too.
c) The curves shown in Figure 4.3 (Figure 11 in the clarification letter response)[5] seem to be different from those in the original CS (Figure 21),[3] i.e. all curves starting from NST are slightly different, most clearly for NST to cGvHD. Surprisingly, in the original model and the model after clarification the same parameter estimates for the various parametric curves are presented. The EAG wonders why the KM curves have changed, and why this change did not translate into a change in the extrapolated curves.

4.2.6.1.3 cGvHD

Transitions from the cGvHD health state were informed from the survival data of the BAT arm of the REACH3 trial. Figure 4.4 presents the KM data from REACH3 that were used to estimate the individual transitions from the cGvHD failure-free health state, whereas Figure 4.5 shows the KM data from REACH3 that were used to estimate the individual transitions from the post-failure health states of cGvHD. The curves with the best statistical fit were selected for each transition. These were the Gompertz for the transition from cGvHD FF to cGvHD NST and exponential model for all other options. An exception to this approach was the transition from relapse to death, for which the log-normal was used which showed the second-best fit, because the long-term predictions based on the Gompertz curve were deemed clinically implausible.

Figure 4.4: Failure-free survival data from REACH3 for each of the individual transitions

Based on Figure 12 of the clarification letter response[5]
BAT = best available therapy; NST = new systemic therapy

Figure 4.5: Post-failure survival data from REACH3 for each of the individual transitions

Based on Figure 13 of the clarification letter response[5]
BAT = best available therapy; NST = new systemic therapy

4.2.6.1.4 General population mortality

Background mortality was used as a lower bound for mortality in each health state. General population mortality was informed from the England and Wales life tables from the period 2017-2019 to exclude the impact of COVID-19.[25] Sex- and age-specific annual probabilities of death were converted to death rates, which were in turn weighted based on the proportion of males in the model and then converted to age-specific probabilities of death per cycle.

4.2.6.1.5 Treatment effect waning

The model includes a setting that allows the incorporation of waning of the treatment effect of ruxolitinib from a certain time point.[5] Effectively, from that time point onwards the transition probabilities for the BAT group are used for ruxolitinib. In the company base-case, no treatment waning was assumed. In a scenario analysis, the company assumed waning of the treatment effect after three years. As they explain in their response to the clarification letter, "*most patients have experienced treatment failure by the end of second year in both the ruxolitinib and BAT arms in REACH2. The impact of treatment waning is minimal after two years. Treatment waning effect has been implicitly captured in the clinical data during the trial period"*.[5]

EAG comment: In the original model, the EAG noticed that including waning of the treatment effect would lead to a lower ICER. When asked in the clarification letter if this was indicative of a modelling error, the company explained that the observed impact of waning could be explained by a smaller

number of patients on ruxolitinib moving to chronic GvHD. They also explained that with the update in the model after clarification (now assuming an equal probability to move to cGvHD for both treatments), the impact of waning is negligible, with the ICER increasing from £25,161 to £25,165 when assuming waning after three years. Some explorative analyses by the EAG show that in the ruxolitinib group the life years decrease slightly when waning is applied whilst at the same time the costs also slightly decrease, resulting in a very similar ICER as without waning. Thus, the EAG is reassured that the issue of waning of the treatment effect will not have an important (or even visible) effect on the cost effectiveness of ruxolitinib.

4.2.7 Adverse events

Treatment related AEs of grade 3 or above, with an incidence rate greater than 2% for either ruxolitinib or BAT were included in the economic model. The AEs with their frequencies as were included in the economic model were based on REACH2 and can be seen in Table 4.6.

Table 4.6: Adverse events (and observed frequency) included in the economic model

AE	Ruxolitinib (REACH2)	BAT (REACH2)
Anaemia	35.53%	24.67%
Thrombocytopenia	33.55%	16.00%
Cytomegalovirus infection reactivation	5.92%	7.33%
Neutropenia	21.71%	12.00%
Oedema peripheral	1.97%	2.00%
Hypokalaemia	10.53%	12.00%
Pyrexia	3.29%	2.67%
Platelet count decreased	17.76%	15.33%
Nausea	0.66%	2.67%
Vomiting	2.63%	1.33%
Diarrhoea	7.24%	5.33%
Hypertension	6.58%	5.33%
White blood cell count decreased	13.16%	8.67%
Abdominal pain	2.63%	3.33%
Acute kidney injury	3.95%	4.67%
Neutrophil count decreased	11.18%	9.33%
Hypoalbuminemia	5.92%	8.00%
Pneumonia	7.89%	8.67%
Sepsis	9.21%	11.33%
Alanine aminotransferase increased	4.61%	3.33%
Urinary tract infection	3.95%	3.33%
Hypocalcaemia	3.29%	4.00%
Hypophosphatemia	4.61%	4.67%
Hyperglycaemia	3.29%	6.00%
Blood bilirubin increased	3.29%	6.00%

AE	Ruxolitinib (REACH2)	BAT (REACH2)
Based on Table 26 in the CS[3] AE = adverse event; BAT = best available therapy; CS = company submission		

EAG comment: In the clarification letter the EAG asked why the AEs observed in REACH3 had not been used to inform AE incidence (Question B12). In their response, the company explained that REACH3 data were not used to inform AEs because the focus of the current submission is aGvHD and *"chronic GvHD was included in the economic model as a subsequent event to capture the full trajectory of the disease. Treatments used for cGvHD are not the intervention or comparator in this analysis and have been excluded from the model. Given the limited impact of AEs in aGvHD, and that the same AEs would be applied in both arms of the model, impact of including AEs in the cGvHD state is expected to be small".*[5]

4.2.8 Health-related quality of life

Health state utility values (HSUVs) were estimated from REACH2 and REACH3. Within these studies, QoL was measured using the EQ-5D-5L. Within REACH2, patient-reported outcomes were administered every week during the first 2 months of the trial and every 4 weeks thereafter until the end of treatment. In REACH3, EQ-5D-5L data was collected on Day 1 of each 28-day cycle up to Cycle 7, then every three cycles from Cycle 9. EQ-5D-3L utilities were obtained by applying the mapping function from Hernández Alava et al. 2020 to the European Quality of Life-5 Dimensions (EQ-5D-5L) responses.[25]

4.2.8.1 Health-related quality of life data identified in the systematic literature review

The full text screening of the SLR only included studies with HSUVs, meaning that articles were excluded if the articles included only non-preference-based HRQoL evidence. A total of 34 publications were included after full-text screening, of which 15 were considered not relevant for the current decision problem because these publications reported on cGvHD alone. Of the other 19 publications, only six publications focused on steroid-refractory aGvHD patients, of which five were based on data from REACH2 and/or REACH3. In five other publications, the population being valued was aGvHD, but was not explicitly described as steroid-refractory, while in six other publications, the population being valued was labelled as GvHD, but was not described as aGvHD or as steroid-refractory. In one of the remaining two publications, a utility value for aGvHD was estimated from proxy conditions such as hepatitis and non-infectious gastroenteritis,[26] while in the other, a utility value was reported for a mixed population including 28.6% GvHD patients.[27] The company considered the five articles based upon the REACH2 study that most aligned with the current decision problem,[28-32] because the EQ-5D instrument was employed, health states were described by patients, the patient population was SR-aGvHD, including some patients from the UK and patients received the treatments relevant for the current decision problem (ruxolitinib or BAT). The other article that reported HSUV from aGvHD steroid-refractory patients also used the EQ-5D-5L, but investigated a different intervention (MSC treatment) and did not include patients from the UK.[33]

EAG comment: Since cGvHD is a health state in the economic model, publications reporting cGvHD utility data are also relevant for the decision problem. In response to Clarification Question B15, the company referred to 15 publications reporting cGvHD utility data (Table 12 in clarification letter response).[5] The company explained that the cGvHD utility data which aligned best with the current decision problem and the NICE reference case were those collected within the REACH3 trial since the

EQ-5D instrument was employed, health states were described by patients, the patient population was steroid-refractory and included some UK patients.

The company referred to the cross-sectional survey in Lachance et al. 2021 where the EQ-5D-5L was also employed, involved valuation of health states by patients with steroid-refractory cGvHD, and included some patients from the UK.[34] The company indicated that the utilities in this study (e.g., 0.69 for steroid-refractory cGvHD) were comparable to those derived from REACH3. In another study (Williams et al. 2023),[35] utilities were obtained using the EQ-5D-5L in an UK vignette study but the values were lower: 0.577, 0.336, and 0.172 for steroid-refractory cGvHD with complete response, partial response, and no response, respectively. The company indicated that in that study, the EQ-5D-5L was filled in by the general public instead of patients and that the authors of the study speculated that "the low utility estimates are partly a reflection of the public's perception of disease severity" and that "patients themselves may learn to cope and adjust over time".),[35] Finally, the company explained that utility values between the REACH3 (ruxolitinib) and the ROCKstar (belumosudil trial) cannot be compared, since the latter values are redacted in the available NICE TA949 documents.[36] Nevertheless, should these be available, the company consider that these would not be directly comparable, given that EQ-5D values were mapped from PROMIS-GH data in the ROCKstar trial and that all trial participants were from the United States of America (USA).

The EAG appreciates the additional information provided by the company but also wonders why only these three studies were chosen for comparison when based on the studies identified and presented in Table 12 of the clarification letter response it seems that more could have been used for validation purposes.

4.2.8.2 Health-related quality of life data used in the cost effectiveness model

Data from REACH2 and REACH3 were pooled all together (both treatment arms in the two trials) to fit a single statistical model to obtain estimates of utility values in each health state. A mixed effects linear model for repeated measurements was fit to utility values at baseline and all other visits where patients completed the EQ-5D questionnaire. Covariates included in the model were baseline utility (centred on the mean) and health state. A covariate for remaining in the FF health state beyond four cycles (112 days) was included in the statistical models because clinical experts highlighted that the mean utility value in REACH2 for the FF health state was lower than expected and it was found that the utility values in the failure-free state improved over time with a stabilisation after cycle 4 (see Table 4.7). Models were fit with and without a random intercept on the subject level.

Table 4.7: Observed utility values for failure-free patients by model cycle

Cycle	Mean EQ-5D-3L	SD	N
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]
8+	[redacted]	[redacted]	[redacted]
Based on Table 29 of the CS[3]			

Cycle	Mean EQ-5D-3L	SD	N
CS = company submission; EQ-5D-3L = EuroQol five-dimension three-level; N = number; SD = standard deviation			

There were only a few observations of utility values in the relapse states with only 16 in REACH2 and nine in REACH3. Therefore, the company also performed analyses which did not include these patients. In that case, the utility for relapsed disease was taken from TA949 (0.479).[36] This gives a total of four models, with and without subject-level random effects (RE) and with and without the relapse state included. Table 4.8 presents a comparison of the utility values included in the model and the average utility value observed for each health state.

Table 4.8: Utility values and goodness-of fit statistics resulting from the different statistical models

Health state	Average health state values	Model 1: With subject level REs	Model 2: With subject level REs without relapse	Model 3: No subject level REs	Model 4: No subject level REs, without relapse
Utility values					
Failure-free, ≤4 cycles	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Failure-free, >4 cycles	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relapse	[redacted]	[redacted]	N/A	[redacted]	NA
cGvHD, failure-free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
cGvHD, NST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
cGvHD, relapse	[redacted]	[redacted]	N/A	[redacted]	N/A
Goodness-of-fit statistics					
AIC	N/A	[redacted]	[redacted]	[redacted]	[redacted]
BIC	N/A	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 31 of the CS[3]
AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; cGvHD = chronic graft-versus-host disease; CS = company submission; N/A = not applicable; NST= new systemic therapy; RE=random effects

Clinical experts consulted by the company indicated that models without subject-level REs seemed more plausible, as they expected patients who remained in the FF state would have comparable QoL to patients with cGvHD. They also considered that the values for relapse from REACH2 and REACH3 seemed too high in comparison to other states, and their preferred analysis was Model 4. Therefore, the company used model 4 in their base-case analysis, with other values tested through scenario analyses. The health state utilities and disutilities used in the model are shown in Table 4.9.

In line with the NICE manual,[37] utility values applied in the model were adjusted for age, using general population utility values for the UK derived from the Health Survey for England (HSE) 2014 dataset reported by Hernández Alava et al. 2022.[38]

Table 4.9: Summary of utility and disutility values used in the base-case cost-effectiveness analysis

State	(Dis)utility value: mean (standard error)	95% CI	Reference in submission (Section and page number)	Justification
Health state utilities				
Failure-free, 4 cycles	[redacted]	[redacted]	Section B.3.4.5, page 111[3]	Based on trial data from REACH2 and REACH3 and in line with clinical opinion
Relapse	[redacted]	[redacted]		TA949[36]
cGvHD, relapse	[redacted]	[redacted]		
Difference in utility compared to Failure-free, first 4 cycles				
Failure-free, >4 cycles	[redacted]	[redacted]	Section B.3.4.5, page 111[3]	Based on trial data from REACH2 and REACH3 and in line with clinical opinion.
NST	[redacted]	[redacted]		
cGvHD, failure-free	[redacted]	[redacted]		
cGvHD, NST	[redacted]	[redacted]		

Based on Table 33 of the CS[3]
cGvHD = chronic graft-versus-host disease; CI = confidence interval; CS = company submission; NST = new systemic therapy; TA = Technology Appraisal

EAG comment: The EAG has several concerns regarding the utility values used for the model health states:

a) The EAG is concerned about the appropriateness of pooling the data from REACH2 and REACH3 to fit a single statistical model to estimate HSUVs because these trials include different patient and disease populations. In response to Clarification Question B13a,[5] the company motivated this choice by stating their preference for a single model for utility with a single variance-covariance matrix, but that data from REACH2 were used to inform utility for the aGvHD states and data from REACH3 were used to inform utility for the cGvHD states. The company also considered it appropriate using utility values from REACH3 for the cGvHD health state as a proxy for those patients with prior aGvHD, since there were [redacted] observations of EQ-5D in patients with cGvHD in REACH2, and the mean utility value for these patients was [redacted]. In REACH3, the mean utility for patients in the FF health state was [redacted]. The company expect that utility values from REACH3 are generalisable to patients with cGvHD in the economic model, which was confirmed by clinical experts. However, the EAG considers that the validity of combining data from different patient and disease populations in one statistical model was not properly justified. In response to Clarification Question B13g,[5] the company also provided separate utility models for REACH2 and REACH3. The EAG considers these models more appropriate, and they are shown in Table 4.10 and 4.11 for aGvHD and

cGvHD, respectively. Although the utility values do not deviate substantially from the utility values from the joint model, the EAG considers it more appropriate to use separate statistical models for the utility values for aGvHD (REACH2) and cGvHD (REACH3). However, as the company did not provide the variance-covariance matrices for these separate models, the EAG is unable to include these in an EAG preferred base-case. Instead, the impact of these models will be explored in Section 6.

Table 4.10: Utility values and goodness-of-fit statistics of a separate model for aGvHD

	Model 1	Model 2	Model 3	Model 4
Failure-free, ≤4 cycles	[redacted]	[redacted]	[redacted]	[redacted]
Failure-free, >4 cycles	[redacted]	[redacted]	[redacted]	[redacted]
NST	[redacted]	[redacted]	[redacted]	[redacted]
Relapse	[redacted]	[redacted]	[redacted]	[redacted]
AIC	–579.0	–579.3	430.9	430.9
BIC	–538.9	–545.0	465.3	459.5

Based on Table 7 of the company response to the clarification letter[5]
aGvHD = acute graft-versus-host disease; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; NST = Next systemic treatment

Table 4.11: Utility values and goodness-of-fit statistics of a separate model for cGvHD

	Model 1	Model 2	Model 3	Model 4
cGvHD, failure-free	[redacted]	[redacted]	[redacted]	[redacted]
cGvHD, NST	[redacted]	[redacted]	[redacted]	[redacted]
cGvHD, relapse	[redacted]	[redacted]	[redacted]	[redacted]
AIC	–3025.7	–3029.8	–1635.9	–1643.1
BIC	–2988.9	–2999.2	–1605.3	–1618.6

Based on Table 8 of the Company Response to the clarification letter[5]
AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; cGvHD = chronic graft-versus-host disease; NST = next systemic treatment

b) Another point of concern is that the choice of the preferred model seems to be based upon clinical expert opinion only. This choice could also be guided by goodness-of-fit statistics. This should be done with caution since not all models have the same number of covariates. For example, the company's preferred model (without relapse) was selected based on clinical expert opinion, but it is not the model with the lowest AIC/BIC.

c) Clinical experts consulted by the company expected that patients who remained in the FF state (for some time) would have comparable QoL to patients with cGvHD. Based on the feedback from these experts and experts consulted by the EAG separately, the EAG considers it likely that this would be true only when the symptoms of aGvHD have been resolved. As mentioned above, patients who remain FF for some time (for example, four model cycles), due to treatment response, are expected to experience an increase in utility over time. It could be assumed that for these long-term responding patients, who still are in FF, the symptoms of aGvHD have been resolved and, therefore, transitioning to cGvHD (for example, after four model cycles) might not be associated with a substantial difference in QoL. However, the main concern of the EAG relates to the substantial increase in QoL for patients who transition from FF aGvHD to cGvHD

within the first four model cycles. Following the previous rationale, it could be assumed that these patients are still experiencing symptoms of aGvHD when transitioning to cGvHD. The EAG considers that a large improvement in the utility value for these patients seems irrational given that these patients are expected to be much sicker, the treatment has not really changed, and response has not been achieved. As the company stated in response to Clarification Question B2a,[5] for acute patients the primary concern is survival, they may experience an extremely poor HRQoL and are often bed-bound. The EAG considers it unlikely that these symptoms will be resolved once patients develop cGvHD in that time period (e.g., before four model cycles). The EAG, therefore, would prefer using a lower utility value for patients in the cGvHD states during the first four model cycles. These should be at least equal to those used for the acute health states, even though it could be argued that these patients might experience even lower HRQoL due to experiencing symptoms of both acute and chronic disease. This is also indicated by the clinical expert consulted by the EAG who said that "*overlap GvHD is frequently omitted from studies but one would expect these patients to have a significantly reduced QoL as well*".[7] In the absence of more specific data, the EAG prefers that the utility values for cGvHD health states in the first four model cycles are equal to the utility values used in the aGvHD health states. The EAG acknowledges that this is a simple assumption, but with the current model structure it is not possible to distinguish between patients with resolved and unresolved acute symptoms.

d) In addition, in Clarification Question B14, the EAG asked the company to compare the utility values in the current appraisal with those in other relevant studies, including TA949, with the expectation that studies where the source of utility data was REACH2 should have similar utilities.[5] The company referred to two prior economic models that have used data from REACH2 and REACH3 to inform utility analyses: the appraisals of ruxolitinib for GvHD by CADTH and Pharmaceutical Benefits Advisory Committee (PBAC).[28, 29] The utility values applied in these models are summarised in Table 4.12 and 4.13. The company explained that the utility data used in these appraisals differed (*slightly*) from the data used in the current submission, since these were based on an earlier data cut, and in both cases EQ-5D-5L values were used directly, instead of using values that have been mapped to the EQ-5D-3L.

Table 4.12: Utility values applied in the CADTH analysis

Health state	aGvHD	cGvHD
Disease baseline	0.47	0.66
Week 4, overall responder	0.51	0.72
Week 4, non-responder	0.42	0.66
Week ≥12, overall responder	0.59	0.75
Week ≥12, non-responder	0.5	0.69

Based on Table 10 of the company response to the clarification letter[5]
aGvHD = acute graft-versus-host disease; CADTH = Canadian Agency for Drugs and Technologies in Health; cGvHD = chronic graft-versus-host disease

Table 4.13: Utility values applied in the PBAC analysis

Health state	aGvHD	cGvHD
Ruxolitinib responders	0.553	0.746
Ruxolitinib non-responders	0.441	0.687
BAT responders	0.553	0.695

Health state	aGvHD	cGvHD
BAT non-responders	0.441	0.636

Based on Table 11 of the Company Response to the clarification letter[5]
aGvHD = acute graft-versus-host disease; BAT = best available therapy; cGvHD = chronic graft-versus-host disease; PBAC = Pharmaceutical Benefits Advisory Committee

The company concluded that despite the difference in the data, the utility values should be comparable across analyses. Even though these prior analyses used models based on response, instead of FFS, and because of that a direct comparison of values should be interpreted with caution, the company considered that in both cases the values for responders (at week 4 in the CADTH model) are close to the values used in the current submission for FF in the first four cycles, and the values for non-responders are also similar to those applied to the NST state in the current model. This was expected, as there is strong correlation between non-response and failure. The EAG agrees with this interpretation, however, it is concerned that in the current submission the utility assumed for FF *after* four cycles is much higher ([redacted]) than the utility for responders in these two appraisals. The company explained that the values used in the CADTH appraisal also included an element of time-dependency, where different values were applied after week 12 (note that in the current appraisal the time point selected is 4 model cycles = 16 weeks). As mentioned above, the value for responders after week 12 is substantially lower than that applied for the FF health state after cycle 4 in the current model, but the company considered that this may be due to the use of the earlier data cut, which may have had fewer observations after week 16. The EAG cannot validate this statement since the number of observations in the CADTH data (earlier data cut) is not reported. In Table 4.7 though it is shown that the sample size of the data used to derive utility values in the current model is greatly reduced already at cycle 3 (12 weeks). Therefore, it is unclear whether a difference in data cut is causing this large difference in utility values. A scenario where the CADTH utility for responders is assumed for FF after four cycles was explored by the EAG in Section 6 of this report.

e) Finally, the company explained that the utility values used in TA949 are redacted due to confidentiality, except for the value applied for the failure state (0.479). This value was initially applied to both NST and relapse health states in TA949, even though it was calculated based on data from patients with relapsed disease only. This assumption was then challenged during the appraisal and the value was only deemed plausible for the relapse health state. As mentioned above, this value was lower than the values estimated for relapsed patients in REACH2 and REACH3, but following advice from clinical experts, it was applied in the company's base-case. Scenarios where the relapse utility was varied according to the values estimated by the company were explored by the EAG in Section 6 of this report.

4.2.8.3 Disutilities due to adverse reactions

Disutilities of Grade 3 or higher AEs with an incidence of ≥2% in REACH2 were included in the model. Adverse event disutilities and associated duration of days were taken from TA949, TA689 and TA642.[36, 39, 40] The QALY loss for each AE was calculated by multiplying the associated disutility with the duration of the AE. A total one-off AE-related QALY loss associated with each treatment was calculated as the sum product of the QALY loss for each AE and the rate of experiencing an AE with a given treatment. Assumed disutilities, AE durations and rate of experiencing an AE can be found in Table 4.14. The one-off AE-related QALY loss is -0.0111 and -0.0088 for ruxolitinib and BAT, respectively.

Table 4.14: Adverse events utility decrements and mean duration applied in model

Adverse event	Mean disutility†	Duration (days)	Frequency ruxolitinib	Frequency BAT	Source
Anaemia	–0.090	23.2	35.53%	24.67%	TA949[36]
Thrombocytopenia	–0.110	23.2	33.55%	16.00%	TA949[36]
Cytomegalovirus infection reactivation	–0.220	14.00	5.92%	7.33%	TA689[40] Infection disutility
Neutropenia	–0.160	15.09	21.71%	12.00%	TA689[40]
Oedema peripheral	–0.195	18.2	1.97%	2.00%	Assumed same as pneumonia
Hypokalaemia	0.000	0.00	10.53%	12.00%	TA642[41]
Pyrexia	–0.195	18.2	3.29%	2.67%	Assumed same as pneumonia
Platelet count decreased	–0.000	0.00	17.76%	15.33%	TA642[41] Assumed no disutility for abnormal lab tests
Nausea	–0.200	3.00	0.66%	2.67%	Assumed same as diarrhoea
Vomiting	–0.200	3.00	2.63%	1.33%	Assumed same as diarrhoea
Diarrhoea	–0.200	3.00	7.24%	5.33%	TA689[40]
Hypomagnesaemia	–0.000	0.00	6.58%	5.33%	TA642[41] Assumed to be the same as hypokalaemia
Hypertension	–0.020	21.0	13.16%	8.67%	TA949[36]
White blood cell count decreased	–0.000	0.00	2.63%	3.33%	TA642[41] Assumed no disutility for abnormal lab tests
Abdominal pain	–0.200	3.00	3.95%	4.67%	Assumed same as diarrhoea
Acute kidney injury	–0.195	18.2	11.18%	9.33%	Assumed same as pneumonia
Neutrophil count decreased	–0.160	15.09	5.92%	8.00%	TA689[40]
Pneumonia	–0.195	18.2	7.89%	8.67%	TA949[36]
Sepsis	–0.195	23.20	9.21%	11.33%	TA949[36]
Alanine aminotransferase increased	–0.050	20.99	4.61%	3.33%	TA689[40]

Adverse event	Mean disutility†	Duration (days)	Frequency ruxolitinib	Frequency BAT	Source
Urinary tract infection	–0.220	14.00	3.95%	3.33%	TA689[40] Infection disutility
Hypocalcaemia	–0.000	0.00	3.29%	4.00%	Assumed same as hypophosphatemia
Hypophosphatemia	–0.000	0.00	4.61%	4.67%	TA642[41] Assumed no disutility for abnormal lab tests
Hyperglycaemia	–0.000	0.00	3.29%	6.00%	TA949[36]
Blood bilirubin increased	–0.000	18.2	3.29%	6.00%	Assumed no disutility for abnormal lab tests

Based on Table 26 and 28 of the CS[3]
†Standard errors were not reported. Assumed to be 20% of the mean in the model, in line with TA949[36]
BAT = best available therapy; CS = company submission; TA = Technology Appraisal

EAG comment: In response to Clarification Question B12,[5] the company explained that hypokalaemia, platelet count decreased, hypomagnesaemia, white blood cell count decreased, hyperglycaemia, and blood bilirubin increased are results of abnormal lab tests and were assumed to have a zero disutility value in line with TA642 and TA949.[36, 41]

Also, the company included in the model the option to select a multiplicative approach to disutilities and explained that the utility multiplier was calculated based on the baseline utility and utility decrements for each AE from Tolley et al. 2013 and Wehler et al. 2018, even though this had a minor impact on the ICER.[42, 43]

4.2.9 Resources and costs

The costs components included in the model are drug acquisition costs of ruxolitinib and BAT, costs of next systemic treatment, costs of cGvHD treatment, health state costs, and adverse event costs.

4.2.9.1 Resource use and costs data identified in the systematic literature review

According to the CS, the SLR identified four studies reporting UK relevant resource use and cost information for aGvHD or cGvHD aged ≥12 years.

Firstly, Dignan et al. 2013 performed a retrospective analysis of 187 patients who underwent an allogeneic HSCT between January 2006 and April 2009 at the Royal Marsden NHS Foundation Trust in the UK.[44] Overall, 118 of the patients developed GvHD, 88 had aGvHD and 58 had cGvHD (not mutually exclusive). Of the 118 patients with GvHD, 61 (52%) were steroid-refractory. The study reports multiple cost outcomes including costs of drugs, radiologic investigations, inpatient stays for transplant, inpatient stays for readmission, and total costs, in addition to HCRU outcomes such as total inpatient days. Data are stratified according to GvHD type and grade (overall GvHD [aGvHD and/or cGvHD] versus Grade I/II aGvHD versus Grade III/IV aGvHD).

Secondly, two National Institute for Health and Care Research (NIHR) Horizon Scanning Research & Intelligence Centre documents, one from 2015 and another from 2016, reported the estimated cost of ECP treatment for steroid-refractory aGvHD, which was >£30,000 over the first 3 months of therapy, and ≤£87,000 over the first year.[45, 46]

Lastly, an NIHR Innovation Observatory document from 2019 reported the NHS indicative cost of ruxolitinib tablets, sourced from the British National Formulary (BNF) in October 2019.[47] A pack of 56 x 5 mg tablets was priced at £1,428.00, while a pack of 56 x 10, 15, and 20 mg tablets was priced at £2,856.00.

EAG Comment: The company only used the costs for inpatients stays for readmissions from Dignan et al. 2013 as cost input for the cost effectiveness model.[44] All other cost components in that study were not relevant for the current decision problem. The company did not use any information from the other three studies identified in the SLR without giving an explanation. However, it does make sense that the company used their own pricing information of ruxolitinib instead of information from the NIHR Innovations Observatory document.

4.2.9.2 Treatment costs (with Patient Access Scheme)

The target dose for ruxolitinib was 10 mg twice daily, but patients who responded to treatment could taper off ruxolitinib from Day 56. Furthermore, doses could be adjusted for safety reasons. To account

for these different doses the average dose per each week for cycle 1, cycle 2, and all subsequent cycles was estimated. The average dose in each week is calculated by dividing the total dose in a specific period by the total treatment exposure (in weeks) in the same period (see Table 4.15). The total dose in a specific time period was derived from time on treatment in the REACH2 study. The total treatment exposure was the total number of weeks that all patients together received ruxolitinib within the specified period.

Table 4.15: Ruxolitinib dose calculations

Period	Cumulative dose	Total dose in period	Treatment exposure in period (weeks)	Average weekly dose (mg)
Day 28	487.3	487.3	3.43	142.2
Day 56	767.5	280.2	2.40	116.6
Day 56 to end of treatment	1350.1	582.6	7.88	73.9
Based on Table 34 of the CS[3] CS = company submission; mg = milligram				

For BAT, the company asked clinical experts to indicate for each treatment the dose as well as the proportion of SR-aGvHD patients receiving it. It was assumed that 3.23% of the patients did not receive any treatment in the BAT arm, similar to the percentage observed in REACH2, and the expert provided proportions were adjusted accordingly. The mean treatment duration was derived from the REACH2 trial. BAT is also the treatment choice for patient in the NST state. The distribution of the different treatments for BAT in the NST state was based upon the distribution of second line treatment as observed in the pooled ruxolitinib and BAT arms of REACH2, excluding the use of ruxolitinib, again adjusted for 3.23% of patients not receiving treatment. Based on clinical expert opinion, the company assumed that the duration of treatment in NST is similar to the duration in the FF state. The dosing regimen, treatment duration and distribution of treatment is reported in Table 4.16.

Table 4.16: BAT dosing assumed in the base-case

Treatments	Dosing regimen	Mean treatment duration (in days)	Proportion of patients in FF state	Proportion of patients in NST state
Anti-thymocyte globulin	3 mg/kg (213 mg) – 7.5 mg/kg (532.5 mg) daily for 3 to 5 days	5.7	0%	11%
Extracorporeal photopheresis	Twice weekly for 4 weeks, then every other week for 10 weeks, then every 4 weeks for up to 1 year	61.7	45%	17%
Mesenchymal stromal cells	N/A		5%	12%
Low-dose methotrexate	7.5 mg/m² per week	29.0	0%	1%
Mycophenolate mofetil	1,000 mg 3 times per day for 28 days	60.0	17%	23%

Treatments	Dosing regimen	Mean treatment duration (in days)	Proportion of patients in FF state	Proportion of patients in NST state
Everolimus	1.5 mg daily[#]	133.5	0%	1%
Sirolimus	Loading dose of 6 mg, then 1–2 mg daily for 12 days	25.0	1%	2%
Etanercept	25 mg twice weekly for 4 weeks, then 25 mg weekly for 4 weeks	51.0	15%	21%
Infliximab	10 mg/kg per week for 4 weeks	37.8	15%	7%
No treatment[*]	–		3%	3%

Based on Table 35, 37 and 38 of the CS[3]

[#] This dosage is strange as the smallest available tablet is 2.5 mg. It might be possible that it is the average of different experts indicating the dosing of everolimus, but the EAG cannot validate this. However, the impact on the total BAT costs is very small as only 1% of the patients receive everolimus as NST.

[*] Expert provided proportions were transformed such that 3% did not receive any treatment both in failure-free and NST state.

BAT = best available therapy; CS = company submission; EAG = Evidence Assessment Group; FF = failure free; mg = milligram; kg = kilogram; NST = next systemic treatment

Unit costs for each treatment are provided in Table 4.17. Drug costs were obtained from the BNF and the electronic market information tool (eMIT).[48, 49] The price per session of ECP was sourced from Button et al. 2021,[50] in line with TA949.[36] Drug wastage was included for infliximab by using the costs of complete vials. The average number of vials was based upon the weight distribution in the REACH2 study. Since there is no list price for MSC available and literature is unclear, two clinical experts gave estimations of the costs of MSC (£12,000 and £20,000). For the base-case analysis, the company used the lower of these values.

Table 4.17: Drug acquisition costs

Treatment	Formulation size	Price per pack (£)	Pack size	Source
Ruxolitinib	10 mg	2,856	56 tablets	BNF[49]
Ruxolitinib ([redacted] price)	10 mg	[redacted]	56 tablets	Company
Anti-thymocyte globulin	25 mg	158.77	1 vial	BNF[49]
Extracorporeal photopheresis	N/A	1,585 per procedure	N/A	TA949[36]
Low-dose methotrexate	2.5 mg	3.18	100 tablets	eMIT[48]
Mycophenolate mofetil	250 mg	9.96	100 capsules	eMIT[48]
Everolimus*	0.75 mg	445.50	60 capsules	BNF[49]
Sirolimus	2 mg	172.98	30 capsules	BNF[49]
Etanercept	50 mg	643.50	4 pre-filled disposable syringes	BNF[49]

Treatment	Formulation size	Price per pack (£)	Pack size	Source
Infliximab	100 mg	755.32	2 pre-filled disposable injection	BNF[49]
Rituximab	1,400 g/11.7 ml	1,344.65	1	BNF[49]
Mesenchymal stromal cells	–	12,000 per treatment course	N/A	Clinical opinion[27]

Based on Table 36 of the CS, with corrections based on response to clarification letter[3]
BNF = British National Formulary; [redacted]; CS = company submission; eMIT = electronic market information tool; mg = milligram; ml = millilitre; N/A = not applicable; TA = Technology Appraisal

The weekly drug acquisition costs were estimated by multiplying the weekly dose with the unit costs and the proportion of patients who received treatment during that week. For each cycle, the relevant weekly costs were summed to estimate the cycle-specific drug acquisition costs.

The company did not include the costs of concomitant steroid use in the model, as steroid use in REACH2 was comparable between arms and so the impact on incremental costs was expected to be minimal.

The company excluded treatment administration costs, because it was assumed that these costs were already included in other cost components. For anti-thymocyte globulin treatment and treatment with MSC, it was assumed that these costs were captured in the cost of initial hospitalisation. The costs of administering ECP is assumed to be captured in the cost estimate from Button et al. 2021.[50]

EAG comment: A few minor issues regarding the estimation of the treatment costs for ruxolitinib and BAT are described below:

a) Drug acquisition costs are based upon costs per mg, while NICE recommends the use of costs per pack. Unfortunately, the EAG cannot adequately correct for this, because crucial information is missing such as the percentage of patients receiving treatment in the hospital over time (where packages are likely to be shared) and the number of weeks dispensed at a time.
b) The company did not include the costs of steroids based on the observation in the REACH2 trial that these were approximately the same for both groups. In general, when there is a difference in mortality between treatment groups, omitting costs that occur in both groups can lead to an over- or underestimation of the ICER. However, in this case, the difference in mortality is small, and the costs associated with steroid use will be low. Hence, the EAG concurs with the approach taken by the company.
c) The cost estimate for MSC treatment was based on clinical expert opinion. Two values were provided (£12,000 and £20,000) of which the company used the lower. In Section B 3.5.1.1 of the company submission, the company indicated that the higher value would be explored in a scenario analysis, however, the results of such scenario were not presented in the company submission.[3] Hence, this scenario will be explored in Section 6.
d) The approach of the company to estimate the drug acquisition costs implicitly includes the tapering of treatment and dose reductions due to safety reasons. As a consequence of this approach, it is not feasible to explore the impact of different tapering strategies.

4.2.9.3 Drug acquisition costs of cGvHD treatment

The distribution of treatments within BAT for the treatment of cGvHD, the dose per week and the treatment duration were derived from REACH3, apart from the treatment duration for belumosudil, which was taken from the median treatment duration as reported in TA949.[36] Furthermore, ibrutinib and infliximab were excluded as clinical experts indicated that these treatment are not used for treating cGvHD in the UK.[21]

For patients who enter the cGvHD NST state, it was assumed that 35% of patients receive ECP and 35% receive belumosudil. The remaining patients receive the other treatments in similar distribution as in the previous line.

Table 4.18: cGvHD treatment costs

	cGvHD, tx. duration (weeks)	cGvHD, tx. dose per week	cGvHD, tx. cost (£)	Incident cGvHD	cGvHD NST
Extracorporeal photopheresis	29.4	Twice per fortnight	46,599.00	47.35%	35.00%
Mycophenolate mofetil	30.2	21,000 mg	61.52	30.20%	17.21%
Sirolimus	39.8	7 mg	803.61	5.99%	3.41%
Everolimus	39.8	10.5 mg	4,139.29	4.35%	2.48%
Rituximab	6.4	500 mg	3,087.89	5.17%	2.95%
Imatinib	32.1	2800 mg	1,565.26	6.94%	3.95%
Belumosudil (list price)	40	1400 mg	62,613.59	0.00%	35.00%
Total cost				**£22,636.12**	**£38,550.48**

Based on Table 39 of the CS[3]
cGvHD = chronic graft-versus-host disease; CS = company submission; mg = milligram; NST = new systemic therapy; tx = treatment

4.2.9.4 Health state costs

The resource use costs for the failure-free and NST states include hospital readmissions and outpatient visits. The company excluded monitoring costs from the model, as they are expected to be similar between arms, in line with TA949.[36]

The frequency of readmissions was derived from REACH2 and is assumed to be the same across the FF and NST states and both arms. In REACH2, there were [redacted] unique readmissions to hospital for patients prior to relapse or death, across 267 patient-years, resulting in [redacted] hospital admissions per year, or [redacted] per 4-week cycle.

The costs for readmissions were taken from Dignan et al. 2013,[44] a single-centre study in which the economic burden of readmissions after an allogeneic HSCT was assessed. Patients with GvHD (including both aGvHD and cGvHD) had on average 2.86 readmissions with total costs of readmissions of £28,860. These costs include the costs for inpatient days, including time spent in critical care, but do not account for outpatient costs. This gives a cost per readmission of £10,091 which the company inflated to £11,786 using the Personal Social Services Research Unit (PSSRU) inflation indices.[51] Based on [redacted] readmissions per 4-week cycle, this yields a cost of £1,006.18 per cycle for readmissions.

The company applied the costs for readmissions also to patients who were hospitalised at the initiation of treatment for SR-aGvHD. Based on the proportion of patients hospitalised in REACH2, it was assumed that in both treatment arms, 14.9% of the patients were hospitalised at time of treatment initiation. Thus, the inpatient costs were increased with 0.149*£11,786=£1,755 in the first cycle. The number of outpatient visits is based on clinical expert opinion. Clinical experts indicated that patients with aGvHD would have outpatient visits every 1-2 weeks, and that these would stop after 3 months for FF patients. In the model, it has been assumed that patients in the FF and NST states would have two outpatient visits per cycle, and that these would stop after three cycles for the FF state. The cost of an outpatient visit is £200.81, which is the weighted average cost of a consultant-led clinical haematology visit from the 2021/22 NHS reference costs (total outpatient attendance service code 303).[52]

In the response to the clarification letter, the company confirmed that tapering off ruxolitinib required additional hospital visits. The company included two additional hospital visits in cycle 4 and 5 for the proportion of patients that tapered off ruxolitinib (31.6%). Health state costs in the cGvHD FF and NST states was taken from a retrospective cohort study by Avenoso et al. 2023 who calculated the costs of HCRU for patients with cGvHD.[53] They found a cost of £17,339 per patient year for inpatient admissions, £4,799 for outpatient appointments and £1,114 for critical care episodes. This gives a total cost of £23,251 per patient-year in cGvHD, or £1,782 per 4-week cycle.

The costs of relapse of the underlying disease was taken from TA949,[36] which used a calculated cost of £2,719.46 per cycle based on TA642.[41] These costs reflect resource use for outpatient visits, emergency department visits, hospitalisation, diagnostic tests, lab tests, and blood transfusion.

An overview of the health state-related costs is shown in Table 4.19.

Table 4.19: Health state-related costs per cycle

Health state	Cost per cycle (£)
Initial hospitalisation (first cycle only)	1,754.59
Failure-free (first 3 cycles)	1,407.80
Failure-free (4th and 5th cycle)	1,133.10
Failure-free (subsequent cycles)	1,006.18
NST	1,407.80
Relapse	2,719.46
cGvHD failure-free	1,782.44
cGvHD NST	1,782.44
cGvHD relapse	2,719.46
Based on Tabel 40 of the CS[3] cGvHD = chronic graft-versus-host disease; CS = company submission; NST = new systemic therapy	

EAG comment: The EAG has a few major points to comment on:

a) There appears to be an error in the company's estimation of the number of hospital admissions per 4-week cycle: [redacted]/267 = [redacted] per patient year and [redacted] per 4-week cycle, rather than the [redacted] per 4-week cycle reported in the company submission. It is unclear to the EAG what the source is of the discrepancy, and thus it is also not clear which of these values is correct. The impact of using the estimate of [redacted] readmissions per 4 weeks will be explored in a scenario analysis in Section 6.

b) The company applied PPSRU inflation rates to index the findings from Dignan et al. to current price levels.[44] The cost per readmission in Dignan et al is £10,091 which was inflated to £11,786. However, using the price year in Dignan of 2010, and indexing to 2023, the correct cost estimate is £13,342[1], which is substantially higher. Based on [redacted] readmissions per 4-week cycle, this yields a cost of £1,134.04 per cycle for readmissions. This corrected value will be applied in the EAG base-case which will be defined in Section 6 of this report.

c) The costs taken from Dignan et el. 2013[44] are not fully representative for the readmission costs for the aGvHD patients in the decision model. The costs in Dignan et al. also include costs of admission due to relapse of the underlying disease, while these relapse treatment costs are separately included in the model. Furthermore, Dignan et al. included a smaller proportion of patients with grade III/IV aGvHD (32% compared to 65% in REACH2 trial),[44] and report that patients with more severe aGvHD have higher readmission costs. Given the information provided by Dignan et al. 2013,[44] it is possible to correct for the different case-mix, leading to higher readmission costs. However, based on the data provided it is not possible to adjust the readmission costs for the inclusion of the relapse costs, but such correction would decrease the readmission cost estimate. Overall, the EAG agrees with the use of the costs as used by the company (but with the correction inflation rate) under the assumption that the underestimation of the costs due to the different case-mix is balanced out by the overestimation of the costs due to the inclusion of relapse readmission costs.

The EAG would also like to note the following (minor) issue:

d) The costs of relapse for AML were included for all relapsed treatments, while only 39% of the patients had AML as underlying disease. The EAG considers that it is not possible to provide a better estimate of these costs, due to the lack of evidence about relapse treatment costs for the other underlying diseases. Although these costs might differ for other malignancies, the EAG expects that it would not have a substantial impact on the ICER as there will not be difference in the probability of relapse between the treatment arms in the EAG base-case.

4.2.9.5 Adverse event costs

The costs of AEs were taken from the literature. The AE cost for each treatment was calculated based on a per-event unit cost and the probability of experiencing AEs from REACH2. Table 4.20 presents the AE costs used in the economic model. The AE costs are applied as a one-off cost to the proportion of patients on treatment at the beginning of the model.

Table 4.20: Adverse events costs

Adverse event	Cost per event (£)	Source	Frequency ruxolitinib	Frequency BAT
Anaemia	410.69	TA949[36]	35.53%	24.67%
Thrombocytopenia	427.06		33.55%	16.00%
Hypertension	543.55		6.58%	5.33%

[1] The EAG had estimated a cost of £14,624 initially. However, during the factual error check, the company pointed out that the EAG had also made an error in the indexing of the 2010 cost for readmission and they provided the correct corrected value.

Adverse event	Cost per event (£)	Source	Frequency ruxolitinib	Frequency BAT
Pneumonia	576.05		7.89%	8.67%
Sepsis	311.58		9.21%	11.33%
Hyperglycaemia	428.03		3.29%	6.00%
Cytomegalovirus infection reactivation	1,955.82	TA689[40]	5.92%	7.33%
Neutropenia	377.81		21.71%	12.00%
Diarrhoea	163.36		7.24%	5.33%
Alanine aminotransferase increased	567.09		4.61%	3.33%
Urinary tract infection	1,955.82		3.95%	3.33%
Hypokalaemia	372.13	TA642[41]	10.53%	12.00%
Neutrophil count decreased	880.67		11.18%	9.33%
Platelet count decreased	2,055.69		17.76%	15.33%
Hypoalbuminaemia	543.55		5.92%	8.005.33%
White blood cell count decreased	574.37		13.16%	8.67%
Hypophosphatemia	372.13		4.61%	4.67%
Oedema peripheral	576.05	Assumed same as pneumonia	1.97%	2.00%
Pyrexia	576.05		3.29%	2.67%
Acute kidney injury	576.05		3.95%	4.67%
Nausea	163.36	Assumed same as diarrhoea	0.66%	2.67%
Vomiting	163.36		2.63%	1.33%
Hypocalcaemia	372.13	Assumed same as hypophosphatemia	3.29%	4.00%
Blood bilirubin increased	0.00	Abnormal lab tests excluded	3.29%	6.00%
Total costs			1,418.72	1,210.71

Based on Table 41 and 26 of the CS[3], with corrections based on Company Factual error check.
BAT = best available therapy; CS = company submission; TA = Technology Assessment

4.2.10 Severity

The NICE reference case stipulates that the committee will regard all QALYs as being of equal weight. The committee may also consider the severity of the condition, as determined by the absolute and proportional QALY shortfall (including discounting at the reference case rate), as decision modifier. Severity can be then taken into account quantitatively in cost effectiveness analyses through QALY weighting, based on the absolute and proportional shortfall, as shown in Table 4.21. Whichever implies the greater severity level will be considered, and if either the proportional or absolute QALY shortfall falls exactly on the cut-off between two severity levels, the higher level will apply.[37]

Table 4.21: QALY weightings for disease severity

QALY weight	Proportional QALY shortfall	Absolute QALY shortfall
1.0	Less than 0.85	Less than 12

QALY weight	Proportional QALY shortfall	Absolute QALY shortfall
1.2	From 0.85 to 0.95	From 12 to 18
1.7	At least 0.95	At least 18
QALY = quality-adjusted life year		

The results of the QALY shortfall analysis are shown in Table 4.22. Total lifetime QALYs were estimated using England and Wales lifetables,[54] and general population utility values for the UK derived from Hernández Alava et al. 2022.[55] The total lifetime QALYs associated with BAT were obtained from the base-case analysis results, and the estimated total QALYs for the general population reflected the baseline characteristics of the REACH2 trial (41% female and 49.5 years). These results suggest that a QALY weight of 1.2 can be applied.

Table 4.22: Summary of company QALY shortfall analysis

Expected total QALYs for the general population	Total expected QALYs for people with BAT	Absolute QALY shortfall	Proportional QALY shortfall	QALY weight
15.86	1.32	14.54	92%	1.2
Based on Table 16 in company's response to clarification letter[5] BAT = best available therapy; QALY = quality-adjusted life year				

EAG comment: The QALY shortfall results presented in Table 4.22 were validated by the EAG. In addition, the disease burden calculator (iDBC) tool also estimates the likelihood of the applicable QALY weight based on the probabilistic sensitivity analysis (PSA) results provided in the company's model, which can be used to estimate the severity adjusted probability of being cost-effective.[56] The QALY shortfall calculations conducted by the EAG were broadly in line with those presented by the company. The uncertainty around the QALY weights shows that there is a 100% estimated probability that the applicable QALY weight is 1.2.

5. Cost effectiveness results

5.1 Company's cost effectiveness results

In Section B.3.9 of the CS,[3] the company presented their CE results by reporting both the ICER and incremental net health benefit (NHB), using the [redacted] price for ruxolitinib and list prices for BAT. To make this Section more concise, the EAG only presents ICERs and not NHB results. Results including comparator Patient Access Scheme (cPAS) prices for BAT will be presented in a separate Appendix to the EAG report.

5.1.1 Main results of the company in the original submission

Table 5.1 shows the company's base-case deterministic CE results for ruxolitinib compared to BAT. Results indicated that ruxolitinib is associated with higher costs and QALYs compared to BAT, accruing [redacted] incremental QALYs and [redacted] additional costs. Using the [redacted] price for ruxolitinib and the comparator list prices, ruxolitinib had an ICER of £33,133 compared with BAT. Once the severity modifier weighting (1.2) has been applied to QALY gains, this reduced to £27,611.

Table 5.1: Company base-case deterministic CE results (deterministic), with [redacted] price

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)	ICER with severity modifier (£/QALY)
BAT	79,632	2.74	1.37	–	–	–	–	–
Ruxolitinib	[redacted]	3.77	[redacted]	[redacted]	1.02	[redacted]	33,133	27,611

Based on Table 46 in the CS[3]
BAT = best available therapy; [redacted]; CE = cost effectiveness; CS = company submission; ICER = incremental cost-effectiveness ratio; Inc. = incremental; LYG = life years gained; QALY = quality-adjusted life years

5.1.2 Main results of the company after the request for clarification

The following changes were made by the company to their base-case after the request for clarification:

- Updated drug costs (in line with the responses to Clarification Questions B19 and C5).[5]
- Same rate of cGvHD incidence in both arms of the model (in line with the responses to Clarification Question B1c).[5]
- Additional monitoring costs for tapering of ruxolitinib (in line with the responses to Clarification Question B18).[5]

Table 5.2 presents the results of the company's updated base-case. The results show that ruxolitinib has higher associated costs and QALYs compared to BAT, resulting in [redacted] incremental QALYs and a total cost increase of [redacted]. Using the [redacted] price for ruxolitinib and reference list prices for BAT, the ICER for ruxolitinib was £30,193 compared with BAT. After applying a severity correction factor weighting of 1.2 to the QALY benefit, the ICER falls to £25,161. Disaggregated discounted QALYs and costs are shown in Table 5.3 and 5.4, respectively.

Table 5.2: Updated company base-case deterministic CE results (deterministic), with [redacted] price

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)	ICER with severity modifier (£/QALY)
BAT	79,292	2.59	1.32	–	–	–	–	–
Ruxolitinib	[redacted]	3.83	[redacted]	[redacted]	1.24	[redacted]	30,193	25,161

Based on Table 7 of company's appendix following the clarification phase[1]
BAT = best available therapy; [redacted] CE = cost effectiveness; ICER = incremental cost-effectiveness ratio; Inc. = incremental; LYG = life years gained; QALY = quality-adjusted life years

Table 5.3: Disaggregated QALYs results (discounted)

Health state	QALY BAT	QALY Ruxolitinib	Increment vs. BAT	Absolute increment	(%) Absolute increment
Failure-free	0.20	[redacted]	[redacted]	[redacted]	[redacted]
New systemic treatment	0.11	[redacted]	[redacted]	[redacted]	[redacted]
Relapse	0.06	[redacted]	[redacted]	[redacted]	[redacted]
cGvHD, failure-free	0.35	[redacted]	[redacted]	[redacted]	[redacted]
cGvHD, new systemic treatment	0.56	[redacted]	[redacted]	[redacted]	[redacted]
cGvHD, relapse	0.05	[redacted]	[redacted]	[redacted]	[redacted]
IV disutility	0.00	[redacted]	[redacted]	[redacted]	[redacted]
AE disutility	-0.01	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs	1.32	[redacted]	[redacted]	[redacted]	[redacted]

Based on updated economic model, following the clarification phase[1]
AE = adverse events; BAT = best available therapy; cGvHD = chronic graft-versus-host disease; IV = intravenous; QALY = quality-adjusted life years

Table 5.4: Disaggregated cost results (discounted), with [redacted] price

Cost item	Cost BAT (£)	Cost Ruxolitinib (£)	Increment vs. BAT (£)	Absolute increment (£)	(%) Absolute increment
Drug acquisition cost	9,352	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment cost	3,037	[redacted]	[redacted]	[redacted]	[redacted]
cGvHD treatment cost	14,652	[redacted]	[redacted]	[redacted]	[redacted]
Administration cost	0	[redacted]	[redacted]	[redacted]	[redacted]
Disease management cost	51,042	[redacted]	[redacted]	[redacted]	[redacted]
AE cost	1,209	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	79,292	[redacted]	[redacted]	[redacted]	[redacted]

Based on updated economic model, following the clarification phase[1]
AE = adverse events; BAT = best available therapy; [redacted]; cGvHD = chronic graft-versus-host disease

Overall, the technology is modelled to affect QALYs by:

- Increasing overall survival (higher number of life years).
- Increasing the number of QALYs in failure-free (aGvHD) and in cGvHD.
- Slightly decreasing the number of QALYs in NST (aGvHD).

Overall, the technology is modelled to affect costs by:

- Its lower acquisition and subsequent treatment costs compared to BAT.
- Increasing disease management and cGvHD treatment costs.
- A minor increase in costs due to AEs.

5.2 Company's sensitivity analyses

5.2.1 Probabilistic sensitivity analysis (PSA)

The company conducted a PSA in which all relevant input parameters were sampled simultaneously from their corresponding probability distributions over 5,000 iterations. The input parameters and the probability distributions used in the PSA can be found in the "Control" sheet of the economic model.[1] The average PSA results are summarised in Table 5.5 and are overall in line with the deterministic ones shown in Table 5.2.

Table 5.5: Company's base-case probabilistic cost effectiveness results (ruxolitinib [redacted] price), after clarification

Technologies	Total Costs (£)	Total QALYs	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	ICER with severity modifier (£/QALY)
BAT	77,811	1.28	–	–	–	–
Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	30,075	25,063

Based on Table 9 of the company's appendix following the clarification phase[57]
BAT = best available therapy; [redacted]; ICER = incremental cost-effectiveness ratio; Inc. = incremental; QALYs = quality-adjusted life years

The company also plotted the PSA outcomes on the CE plane, as shown in Figure 5.1. [redacted]. From the PSA results, cost effectiveness acceptability curves (CEAC) were also calculated and shown in Figure 5.2. The CEAC plot indicates that ruxolitinib was dominant in [redacted] of the simulations and was cost-effective in [redacted] and [redacted] of the simulations at common willingness-to-pay (WTP) thresholds of £20,000 per QALY and £30,000 per QALY gained, respectively.

Figure 5.1: PSA CE-plane (ruxolitinib [redacted] price, without severity modifier)

[redacted]

Based on Figure 1 of the company's appendix following the clarification phase[57]
BAT = best available therapy; [redacted] CE = cost effectiveness; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Figure 5.2: PSA CEAC (ruxolitinib [redacted] price, without severity modifier)

[redacted]

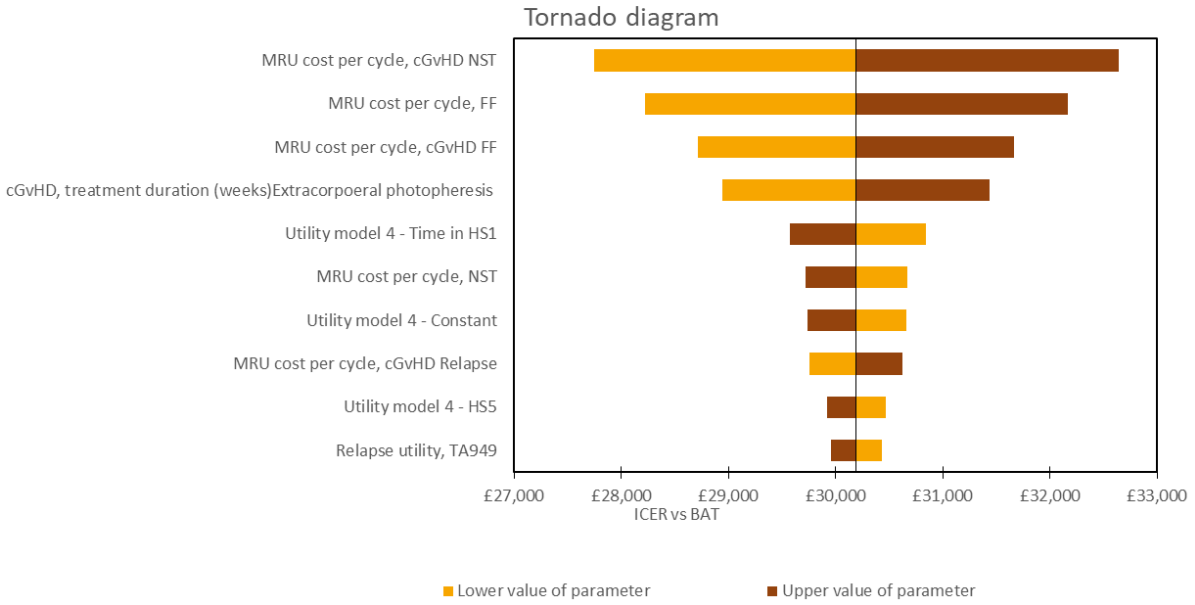
Based on Figure 1 of the company's appendix following the clarification phase[57]
BAT = best available therapy; [redacted] CEAC = cost effectiveness acceptability curve; PSA = probabilistic sensitivity analysis

5.2.2 Deterministic sensitivity analysis (DSA)

The company also conducted DSAs where all input parameters were varied using as higher and lower values the 95% confidence intervals. For input parameters for which there were only a point estimate value available in the model, the higher and lower values were determined using ±20% of their mean base-case value. Figure 5.3 presents the tornado diagram of the ten most influential parameters on the ICER of ruxolitinib versus BAT. Overall, most input parameters have a minor impact on the model results, except for the cost of MRU and the utility values used the model. Although results were mostly

influenced by the changes in these inputs, changes in ICER were deemed relatively modest by the company.

Figure 5.3: DSA tornado diagram for ICER (ruxolitinib [redacted] price, without severity modifier)



Based on Figure 3 of the company's appendix following the clarification phase[57]
[redacted] cGvHD = chronic graft-versus-host disease; DSA = deterministic sensitivity analysis; FF = failure-free; HS = health state; ICER = incremental cost-effectiveness ratio; MRU = medical resource use; NST = new systemic therapy; TA = Technology Appraisal

5.2.3 Scenario analysis

The company presented 27 scenario analyses to assess the robustness of the model results to changes in some modelling assumptions. A summary of the results of these scenarios is provided in Table 5.6. These included the following:

- Exploring alternative time horizon (20 years) and discount rates (0%).
- Different approach to estimating transition probabilities (naïve analysis instead of crossover), several choices of survival curves extrapolation and treatment effect waning.
- Assuming different statistical models for utilities, using cGvHD utility from TA949 and a multiplicative approach for disutilities.
- Alternative BAT distributions, exclusion of resource use costs for GvHD, changing the proportion of belumosudil (65%) for third-line cGvHD and no additional monitoring for tapering of ruxolitinib.

In general, the modelling assumptions explored by the company had a minor impact on the ICER. Only the scenarios where different GvHD resource use/costs were not included resulted in very low ICERs. On the opposite direction, no scenarios resulted in a severity weighted ICER above the common thresholds used by NICE.

Scenarios where the BAT distribution is changed should also impact QALYs, since some of the options included in BAT seem to be more effective than others. However, this is not possible in the model, where changes in the BAT distribution only affects costs.

Table 5.6: Summary of company scenario analyses (ruxolitinib [redacted] price)

Description base-case	Description Scenario	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	ICER (£/QALY) with severity modifier
Base-case	-	[redacted]	[redacted]	30,193	25,161
Decision problem					
Lifetime	Time horizon = 20 years*	[redacted]	[redacted]	29,969	24,974
3.5% for both	No discounting	[redacted]	[redacted]	31,549	26,291
Clinical data					
Transition probabilities estimated following adjustment for crossover	Transition probabilities from the naïve analysis	[redacted]	[redacted]	31,299	26,082
Choice of extrapolation curves guided by clinical input	Best fitting models based on AIC/BIC	[redacted]	[redacted]	30,531	25,443
Apart from the transition from FF to cGvHD, joint models were used for the other FF transitions	Individual models for all FF-state transitions; changed extrapolation options based on statistical fit (remaining transitions per base-case)	[redacted]	[redacted]	29,530	24,608
	Individual models for all FF-state transitions; changed extrapolation options based on clinical input (remaining transitions per base-case)	[redacted]	[redacted]	33,484	27,904
	Joint models for all FF-state transitions; changed extrapolation	[redacted]	[redacted]	27,641	23,034

Description base-case	Description Scenario	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	ICER (£/QALY) with severity modifier
	options based on statistical fit (remaining transitions per base-case)				
	Joint models for all FF-state transitions; changed extrapolation options were selected clinical input (remaining transitions per base-case)	[redacted]	[redacted]	33,044	27,537
Models based on pooled data	Joint models for post-failure outcomes	[redacted]	[redacted]	28,161	23,468
No waning	Treatment waning after Year 3	[redacted]	[redacted]	30,198	25,165
Utilities					
Model 4 without subject-level RE and without the relapse state included.	Average observed utility values	[redacted]	[redacted]	28,476	23,730
	Mixed effects model	[redacted]	[redacted]	32,110	26,758
	Mixed effects model, without relapse	[redacted]	[redacted]	32,228	26,857
	Fixed effects model	[redacted]	[redacted]	30,000	25,000
	cGvHD utility from TA949	[redacted]	[redacted]	31,940	26,617
Costs and resource use					
BAT distribution as reported in Table 4.4.	ECP only for BAT	[redacted]	[redacted]	22,695	18,912
	BAT per clinician survey	[redacted]	[redacted]	27,213	22,678
	ECP @ 60%	[redacted]	[redacted]	28,233	23,528
	ECP @ 80%	[redacted]	[redacted]	25,464	21,220
	BAT per REACH2	[redacted]	[redacted]	33,608	28,006

Description base-case	Description Scenario	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	ICER (£/QALY) with severity modifier
	2L BAT = 1L BAT	[redacted]	[redacted]	28,443	23,702
Resource use costs for GvHD included	No resource use costs	[redacted]	[redacted]	144	120
cGvHD scenarios					
Resource use costs for cGvHD included	No costs for cGvHD	[redacted]	[redacted]	2,020	1,684
	No resource use for cGvHD	[redacted]	[redacted]	8,411	7,009
35% receive BEL	BEL for 65% of 3L cGvHD	[redacted]	[redacted]	32,493	27,078
	BEL only for 3L cGvHD	[redacted]	[redacted]	33,192	27,660
Additional scenario analyses to accompany the response to Clarification Questions					
Tapering of ruxolitinib	No additional monitoring for tapering of ruxolitinib	[redacted]	[redacted]	29,815	24,846
No waning	Treatment waning from Year 2	[redacted]	[redacted]	30,196	25,164
Model 4 without subject-level RE and without the relapse state included.	Separate utility analyses, Model 1	[redacted]	[redacted]	32,363	26,969
	Separate utility analyses, Model 2	[redacted]	[redacted]	32,485	27,071
	Separate utility analyses, Model 3	[redacted]	[redacted]	29,975	24,979
	Separate utility analyses, Model 4	[redacted]	[redacted]	30,165	25,138
Disutilities: additive approach	Multipliers for AE disutilities	[redacted]	[redacted]	30,173	25,144

Based on Table 11 and Table 13 of the company's appendix following the clarification phase[57]
* This result was corrected in response to the company Factual error check.

Description base-case	Description Scenario	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	ICER (£/QALY) with severity modifier
1L = first-line; 2L = second-line; 3L = third-line; AE = adverse events; AIC = Akaike Information Criterion; BAT = best available therapy; BEL = belumosudil; BIC = Bayesian Information Criterion; [redacted]; cGvHD = chronic graft-versus-host disease; ECP = extracorporeal photopheresis; FF = failure-free; ICER = incremental cost-effectiveness ratio; Inc. = incremental; QALY = quality-adjusted life year; RE = random effects; TA = Technology Appraisal					

5.3 Model validation and face validity check

The validation efforts conducted on the economic model were discussed in the validation section of the CS (B.3.13).[3] These mostly referred to the implementation of feedback from UK clinical experts (five consultant haematologists) and a health economist, and technical verification. Validation feedback from experts was gathered during individual validation teleconferences, and an advisory board. The following key topics were discussed: validation of BAT treatments and their distributions in UK clinical practice, the dosing schedules of treatments within BAT, value of FFS as a clinical endpoint, appropriateness of the model structure, key model inputs and assumptions, plausibility of survival extrapolations and model prediction for FFS and OS, and how ruxolitinib is used within UK clinical practice. The individual teleconference reports and the advisory board report are included in the reference pack of this submission.[20, 21] In addition, more details about model validation were provided by the company in response to some Clarification Questions.[5] In the remaining of this Section, the validation efforts performed on the model, as presented by the company, are categorised according to the types of validation used in the Assessment of the Validation Status of Health-Economic decision models (AdViSHE) tool.[58]

5.3.1 Validation of the conceptual model

5.3.1.1 Face validity testing (conceptual model)

The company indicated that the appropriateness of the model structure was one of the key topics discussed with the experts during the individual teleconference calls and the Advisory Board.[20, 21]

5.3.1.2 Cross-validity testing (conceptual model)

The previous belumosudil for cGvHD NICE appraisal TA949 was used to cross-validate some model assumptions around the inclusion of chronic patients in the economic model. The main differences with respect to the company's approach in TA949 are the following:

- In the current submission, the chronic part of the model is subdivided into three health states (failure-free, NST and relapse), whereas in TA949 a single health state to represent cGvHD was used. The company justified the current approach based on the heterogeneity of the outcomes with cGvHD, for example much poorer for patients who relapse compared to those that require additional systemic treatment (this was highlighted as a key issue in TA949).
- In TA949, a partitioned survival model (PSM) based on FFS was used, which included failure-free, failure, and death as health states. FFS was considered a relevant endpoint for the model. However, time in the failure health state was calculated as the difference between FFS and OS, which does not account for differences in costs and QALYs of patients experiencing clinically distinct events that define FFS in the trials. For this reason, a PSM approach was not considered accurate enough by the company to reflect the natural history of the GvHD.

Additional details were provided by the company in response to Clarification Question B25,[5] where it was explained that the model structures used in Ong et al. 2023, and the CADTH and PBAC reports from 2022 were based on response to treatment.[28, 29, 59] However, this approach of using response together with FFS was criticised by NICE in TA949, resulting in response being removed from the model and the EAG suggesting modelling failure events as separate health states.[18] Furthermore, the model used in the current submission also allows for explicit consideration of patients who develop cGvHD. A similar model structure was used in James et al. 2019 where FFS instead of response was considered.[60]

In conclusion, the company considered that previous models based on response do not account for different mechanisms of failure, and, therefore, their impact on costs, QoL and mortality. Overall survival is simply extrapolated based on response, without capturing time to next treatment or relapse. Duration of response is modelled and patients with a response can move to non-response, but relapse and time to NST are not explicitly included in these models. The company considered extrapolating outcomes based on FFS more plausible than doing it based on response, as it explicitly accounts for the mechanism of failure when assessing costs, QoL and mortality.

5.3.2 Input data validation

5.3.2.1 Face validity testing (input data)

Key model inputs were also reviewed by the experts consulted by the company.[20, 21] These included at least BAT treatments and their distributions in UK clinical practice, the dosing schedules of BAT treatments, survival curves extrapolations, treatment duration in the NST health state, belumosudil usage, or utility values.

In Clarification Question B14,[5] the EAG asked the company to compare the utility values in the current appraisal with those in other relevant studies including TA949. We refer to the EAG comment in Section 4.2.8 of this report for details.

In addition, in Clarification Question B18, the EAG queried the fact that no costs had been incorporated for monitoring the tapering of ruxolitinib.[5] In response, the company incorporated these costs into the model. These changes had a very small impact on the outcomes.

In Clarification Question B1c,[5] the EAG asked what the underlying reason was for having more patients developing cGvHD in the ruxolitinib arm, and if it is something to be observed in real practice. In the process of responding to this question, the company sought clinical validation and they indicated that they did not expect the incidence of cGvHD to be different between BAT and ruxolitinib (after accounting for the competing events) and that it would be more appropriate to assume the same incidence in both arms. Consequently, the company updated the model base-case to the same rate of cGvHD for both arms, estimated form the pooled ruxolitinib and BAT data from REACH2.

The EAG noticed (as explained in Section 4.2.9.4) that the cost per readmission from price year 2010 (£10,091) was inflated to £11,786. However, when indexing to 2023, this estimate should be £13,342 (see also footnote Section 4.2.9.4).

5.3.2.2 Model fit testing

The company mentioned in the CS that "*validation was undertaken using the individual models fit to the BAT data, as the patterns of survival for BAT with each curve are comparable between the individual and joint models, and the choice of curves is not affected by the switch to joint models*".[3] It should be noted that it seems that models fit to ruxolitinib data were not validated, or the validation efforts were not reported in the CS.

Furthermore, the curves shown in Figure 4.3 (Figure 11 in the clarification letter response)[5] seem to be different from those in the original CS (Figure 21).[3] Also, all curves starting from NST are slightly different, most clearly for NST to cGvHD. However, in both models the same parameter estimates for the extrapolation curves are presented. The EAG wonders why the KM curves have changed, and why this change did not translate into a change in the extrapolated curves, which in turn might question their validity.

5.3.3 Validation of the computerised model (technical verification)

The company explained that quality control of the economic model was performed by both the model developers and by external health economists not involved in the development of the model. These validation exercises included cell-by-cell and logical checks, and stress testing using a predefined list of tests. Details are provided below.

5.3.3.1 External review

Verification of model implementation were also performed by health economists not involved in the model development, but it is not mentioned how many. This was done in accordance with a predefined test plan, but details of this plan were not reported by the company.

Despite the verification efforts reported by the company, the EAG identify some errors/issue before and after clarification.

Before clarification, the EAG found various small errors relating to the drug acquisition costs for BATs which the company corrected. These errors had a minimal impact.

After clarification some errors were found on the "Survival Data" sheet of the model, where for all three transitions starting from NST, selecting the joint distribution led to a different constant for the gamma distribution for BAT and ruxolitinib. The EAG has corrected this for the EAG base-case (see Section 6.1.1). Furthermore, the EAG found that on the "Control" sheet of the model, the pooled distributions starting from failure-free were not included, which means that when these curves are selected, the PSA does not incorporate the associated uncertainty. Thus, the EAG added the coefficients of these pooled curves to the PSA.

5.3.3.2 Extreme value testing

Stress testing was conducted using a predefined list of tests. However, details on this list and the results of the tests were not provided by the company in the CS.

5.3.3.3 Testing of traces

The company also indicated that the implementation of the health state membership calculations in Visual Basic for Applications (VBA) was validated by calculating the health state membership using sheet functions for the first five cycles to ensure these aligned. Five cycles were selected to allow for transitions into and out of every model health state to be tested. Traces can be found in the model engine sheets.

5.3.3.4 Unit testing

The company indicated that technical verification included cell-by-cell and logical checks, and stress testing using a predefined list of tests. It is not mentioned if the complete VBA code was also validated or not.

5.3.4 Operational validation (validation of model outcomes)

5.3.4.1 Face validity testing (model outcomes)

Although it is not explicitly mentioned in the CS (the company only referred to plausibility of model prediction for FFS and OS), the EAG assumed that model results were presented to experts who provided some extent of validation for the model results, but this should be confirmed by the company.

5.3.4.2 Cross validation testing (model outcomes)

5.3.4.2.1 Comparisons with other technology appraisals

This type of validation was not reported by the company.

5.3.4.2.2 Comparisons with other models (not necessarily technology appraisals)

In response to Clarification Question B23,[5] the company compared the QALYs for BAT and ruxolitinib in the current submission with those from previous cost-effectiveness analyses. This is summarised in Table 5.7.

The company concluded that the analyses conducted in the current submission resulted in more QALYs for both BAT and ruxolitinib compared to previous analyses. The company explained that all prior analyses employed a model structure around treatment response, where OS was extrapolated based on response status, instead of using FFS as in the current submission. However, the company also considered that the difference in model structure would not completely explain the difference in QALYs, which would be driven by differences in the survival data used, because, since the publication of these models, additional follow-up from REACH2 have become available, with more data available on OS. For example, the company indicated that in the previous analyses, OS data were available up to 24 months, and the modelled survival was lower than in the analysis conducted for the current submission. In the PBAC model, OS for ruxolitinib was 30% at year 2 and 20% at year 3, whereas this was 20% and 12% for BAT at year 2 and year 3, respectively. In the CADTH report, survival estimates were presented by response status, where responder OS was approximately 40% at year 2, and slightly under 30% at year 3. However, using the data cut considered in the current submission, OS for the ruxolitinib arm was 40% at year 2 and remained at 40% at the end of follow-up. The company consider that this increase in survival is what drives the increase in QALYs predicted in the current submission.

In line with this, in Clarification Question B24,[5] the EAG asked the company to explain why on page 11 of the CS, it is mentioned that patients with SR-aGvHD have poor survival (only 25% of patients alive two years after diagnosis, decreasing further to 10% at four years), but in the model [redacted]% of BAT patients were alive at year 2, and [redacted]% of ruxolitinib patients. The company explained that the literature figures were sourced from Westin et al. 2011 and Rashidi et al. 2019,[61, 62] where Westin et al. 2011 included data on transplant performed between 1998 and 2002, and Rashidi et al. 2019 used data on transplant between 1990 and 2016, with 69% of transplants occurring before 2005. The company expect that improvements in OS have occurred since then. In addition, the company stressed that the modelled OS for BAT was very similar to the observed data, where the KM survival at the end of follow-up was 30.6%, compared with [redacted]% in the model. Overall survival at the end of follow-up in the ruxolitinib arm of REACH2 was 38.7%, compared with [redacted]% in the model. Extrapolations of OS were presented to clinicians, who agreed that the extrapolations seemed reasonable, and the OS results predicted by the model expected to be valid. The company referred to James et al. 2019 where a similar model structure based on FFS instead of response was considered.[60] It could have been useful then comparing the results in this submission with those in this study.

Table 5.7: Total QALYs comparison in current submission with previous cost-effectiveness analyses

	PBAC model[29]	CADTH model[28]	Ong et al. 2023[59]	Current submission
BAT QALYs	0.62	0.92	0.89	1.32
Ruxolitinib QALYs	0.84	1.07	1.04	[redacted]
Incremental	0.22	0.15	0.15	[redacted]

Based on Table 13 in clarification letter response and updated economic model, following clarification[1, 5]
* In Table 13 of the clarification letter response, the company reported the values from the original CS ([redacted] QALYs for ruxolitinib and 1.37 for BAT). The values shown now correspond to those in the model after clarification
BAT = best available therapy; CADTH = Canadian Agency for Drugs and Technologies in Health; CS = company submission; PBAC = Pharmaceutical Benefits Advisory Committee; QALY = quality-adjusted life year

It is unclear why a similar exercise was not attempted to validate the life years, or the total costs estimated by the model. The difference is in QALYs with respect to previous analyses indicates that the difference in life years could be substantial also in the BAT arm. Since, as shown in Table 5.4, BAT acquisition costs are [redacted] than those for ruxolitinib, total BAT costs would [redacted] in the current submission, which may have a substantial impact on the ICER.

As mentioned above, it would have also been valuable to ask experts to validate the model results, but it is unclear whether this has been done or not.

5.3.4.3 Validation against outcomes using alternative input data

This type of validation was not explicitly reported by the company unless it was considered part of the scenario analyses.

5.3.4.4 Validation against empirical data

5.3.4.4.1 Comparison with empirical data used to develop the economic model (dependent validation)

This type of validation was not reported by the company.

5.3.4.4.2 Comparison with empirical data not used to develop the economic model (independent validation)

This type of validation was not reported by the company.

6. Evidence Assessment Group's additional analyses

6.1 Exploratory and sensitivity analyses undertaken by the EAG

Table 6.1 summarises the CE key issues categorised according to the sources of uncertainty as defined by Grimm et al. 2020:[63]

- Transparency (e.g., lack of clarity in presentation, description, or justification)
- Methods (e.g., violation of best research practices, existing guidelines, or the reference case)
- Imprecision (e.g., particularly wide CIs, small sample sizes, or immaturity of data)
- Bias and indirectness (e.g., there is a mismatch between the decision problem and evidence used to inform it in terms of population, intervention/comparator and/or outcomes considered)
- Unavailability (e.g., lack of data or insight).

Identifying the uncertainty sources can help determine the course of action to be taken (i.e., whether additional clarifications, evidence and/or analyses might help to resolve the key issue).

Table 6.1 also lists alternative approaches, expected effects on the CE estimates, whether it is reflected in the EAG exploratory analyses, or if additional evidence or analyses might help resolving the identified key issues.

6.1.1 Explanation of the EAG adjustments for the EAG base-case

Based on all considerations in the preceding Sections of this EAG report, the EAG made various adjustments to the company's model after clarification (Table 5.2). These adjustments made by the EAG form the EAG base-case and can be subdivided into three categories (derived from Kaltenthaler et al. 2016):[64]

- Fixing errors (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (correcting the model where the EAG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (amending the model where the EAG considers that reasonable alternative assumptions are preferred).

6.1.1.1 Fixing errors

In the current assessment a few errors were found in the electronic model after clarification that the EAG fixed.

1. After clarification some errors were found on the "Survival Data" sheet of the model, where for all transitions starting from NST and relapse, selecting the joint distribution led to a different constant for the gamma distribution for BAT and ruxolitinib.[2] The EAG has corrected this for the EAG base-case.
2. The EAG found that on the "Control" sheet of the model, the pooled distributions starting from failure-free were not included, which means that when these curves are selected, the PSA does

[2] The following cells were changed on "Survival data": K95, K117, K139, K161, BS95, BS117, BS139 and BS161

not incorporate the associated uncertainty. Thus, the EAG added the coefficients of these pooled curves to the PSA.

3. The company applied PPSRU inflation rates to index the cost per readmission from Dignan et al. to current price levels.[44] The cost from Dignan is £10,091 which was inflated to £11,786. However, using the price year in Dignan of 2010, and indexing to 2023, the cost estimate comes to £13,342, which is substantially higher (see also footnote Section 4.2.9.4). Based on [redacted] readmissions per 4-week cycle, this yields a cost of £1,134.04 per cycle for readmissions. Note that the revised cost estimate is also used for the proportion of patients that are in hospital at the start of the model.

6.1.1.2 Fixing violations

The company used an additive approach to disutilities whereas the NICE methods guide states a preference for a multiplicative approach. Thus, the latter is selected for the EAG base-case.[37]

6.1.1.3 Matters of judgement

The EAG's preferences regarding alternative assumptions led to the following changes to the company base-case analysis:

1. As explained in Section 4.2.6.1.1, the company's approach to survival data extrapolation lacks consistency, which in some cases results in implausible and/or contradictory decisions. A simple way to overcome some of these issues could be adopting a pragmatic approach where the only benefit of ruxolitinib over BAT would be on delaying time to NST. For the other transitions, acknowledging the outstanding uncertainties, the EAG has made the assumption that they can be considered equal between both arms.
2. In Section 4.2.8.2 it was discussed that the EAG has some reservations about the utility associated with the cGvHD health state ([redacted]) compared to the utility for the first four cycles in failure-free aGvHD ([redacted]). When patients remain failure-free for some time (for example, four model cycles) it is reasonable to assume they experience an increase in utility over time. It could be assumed that for these patients, who still are in failure-free, the symptoms of aGvHD have been resolved and, therefore, transitioning to cGvHD (for example, after four model cycles) might not be associated with a substantial difference in QoL, though an initial decrease in utility would be more plausible. However, the main concern of the EAG relates to the substantial increase in QoL for patients who transition from failure-free aGvHD to cGvHD within the first four model cycles. Following the previous rationale, it could be assumed that these patients are still experiencing symptoms of aGvHD when transitioning to cGvHD. The EAG considers that a large improvement in the utility value for these patients seems irrational given that these patients are expected to be much sicker, the treatment has not really changed, and response has not been achieved. The EAG, therefore, prefers using a lower utility value for patients in the cGvHD states during the first four model cycles. This utility should at most be equal to the utility for aGvHD in the first four cycles, though it could be argued that these patients might experience even lower HRQoL due to experiencing symptoms of both acute and chronic disease. To address some of the EAGs reservations about the utility values for cGvHD health states, in the first four model cycles the failure-free cGvHD utility is assumed to be equal to the utility value in the failure-free aGvHD health state.

6.1.2 EAG exploratory scenario analyses

The EAG conducted two sets of scenario analyses to explore the impact of key assumptions and uncertainties within the CE analyses that were not explored in the company defined scenarios. While

the main focus was on the key issues described in Table 6.1, other uncertainties were also explored. A description of these scenario analyses is provided below.

6.1.2.1 Scenario analyses set 1: there is uncertainty in the derivation and implementation of HRQoL in the model

6.1.2.1.1 Acute GvHD failure-free long-term health state utility values higher than those of chronic patients

One clinical expert consulted by the EAG considered that "*patients who suffer acute GvHD that resolves will overall be expected to have a significantly better QoL, and decreased health care usage than patients who go on to develop chronic GvHD. This is true irrespective of whether the chronic GvHD patient had prior acute GvHD*". The EAG interpreted that long-term utilities for FF aGvHD could be higher than those of chronic patients. Therefore, the EAG explored the scenario of reducing the cGvHD FF utility by 20%. Note that this value is arbitrary and therefore, the results of this scenario should be considered exploratory only. Note also that, in order to avoid inconsistencies between HSUVs, the utility value of the cGvHD NST health state has to be reduced as well (otherwise it would be higher than FF [Change in "Utility data" – Cells H14 and H15]).

6.1.2.1.2 Equal utility value for acute and chronic GvHD NST health states

To the question "*would you expect the quality of life for aGvHD patients that require a second/third line of systemic therapy to be different than for cGvHD patients once aGvHD is resolved that require a second/third line of systemic therapy?*", the first clinical expert consulted by the EAG indicated that these should not be too different, whereas the second expert explained that this would depend on the severity of the chronic disease. In the company's model, the utility values used for chronic NST is higher than the values used for acute NST. The EAG explored the scenario of assuming these to be equal. Note that this is arbitrary and, therefore, the results of this scenario should be regarded as exploratory (Change in "Utility data" – Cell H15).

6.1.2.1.3 Separate statistical models for the utility values for aGvHD (REACH2) and cGvHD (REACH3)

As explained in the EAG comment of Section 4.2.8.2, the EAG considered using separate utility models for aGvHD and cGvHD more appropriate. However, as the company did not provide the variance-covariance matrices for these separate models, the EAG was unable to include these in an EAG preferred base-case. Therefore, the impact of these models is explored in this Section.

6.1.2.1.4 Alternative source for FF utility

As explained in the EAG comment of Section 4.2.8.2, the EAG was uncertain whether a difference in data cut was causing the large difference in utility values observed for the FF health state compared to the CADTH study. A scenario where the CADTH utility for responders after 12 weeks (0.59) is assumed for failure-free after four cycles was explored by the EAG in this Section (Change in "Utility data" – Cell H11).

6.1.2.2 Scenario analyses set 2: resource use and costs

6.1.2.2.1 BAT only consisting of ECP treatment

The clinical expert that was consulted by the EAG indicated that ECP is the preferred treatment option in a world without ruxolitinib. Therefore, the EAG also performed a scenario in which BAT only consisted of ECP treatment (Change in Sheet Cost data Cell C20:C28).

6.1.2.2.2 Higher and lower overall costs of BAT treatment

The distribution of the different BAT treatments and the dosing schedule was completely based upon clinical expert opinion. The EAG decided to decrease and increase the overall costs of BAT treatment per cycle with 25% to explore any impact of the costs of BAT treatment on the ICER (Change in Sheet Bat Costs AH4:AH55).

6.1.2.2.3 Costs for readmissions with a readmission rate of [redacted] instead of [redacted]

Based upon the information provided by the company, the EAG estimated a readmission rate of [redacted] instead of [redacted]. This readmission rate has an impact on the disease management costs in the FF and NST health state (Change in Sheet Cost data C65 and C66).

6.1.2.2.4 Costs for MSC treatment high estimate clinical expert

Since there is no list price for treatment with MSC available and literature is unclear, two clinical experts gave estimations of the costs of MSC (£12,000 and £20,000). For the base-case analysis, the company used the lower of these values, in this scenario the impact of the higher estimate will be explored (Change in Sheet Cost data E22).

6.1.3 EAG subgroup analyses

No subgroup analyses were performed by the EAG.

Table 6.1: Overview of key issues related to the cost effectiveness (conditional on fixing errors highlighted in Section 5.1)

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in EAG base-case[b]	Required additional evidence or analyses
The EAG considers that the likely mixture of patients (in terms of treatment response and/or resolution of symptoms) in the FF health states is not completely captured in the model	4.2.2	Bias & indirectness Unavailability Transparency	Alternative transition probabilities, utilities and costs conditional on symptoms resolution	+/-	No	Data collected on different subgroups allowing estimation of input parameters by symptom resolution.
The EAG is uncertain about the modelling of patients with chronic disease since the chronic population in the model and the population in REACH3 do not completely align	4.2.3	Bias & indirectness	Alternative transition probabilities (and possibly utilities and costs) for the modelled chronic population	+/-	No	Evidence supporting the alignment of the chronic population in the model and in REACH3. If necessary, re-estimation of all model parameters for the chronic population.
The EAG does not agree (in general) with the choices made by the company to extrapolate (FF) survival data	4.2.6	Methods Transparency	Alternative fitted parametric models for time to events (used to derive transition probabilities)	+/-	Partial/Explored	Similarity assessment between the populations in the model and in the clinical trials. Reassessment of the survival analysis in a consistent and systematic way, avoiding implausible

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in EAG base-case[b]	Required additional evidence or analyses
						and/or contradictory decisions.
The EAG is uncertain about the implementation of health state utilities (some of the health state utility values and some modelling assumptions)	4.2.8	Bias & indirectness Transparency	Alternative fitted regression models for utilities	+/-	No/Explored	Similarity assessment between the populations in the model and in the clinical trials. Reassessment of the regression analyses.

[a] Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the EAG and '+' indicates that the EAG believes this issue likely induces bias in favour of the intervention versus at least one comparator
[b] Explored
EAG = Evidence Assessment Group; FF = failure-free; ICER = incremental cost-effectiveness ratio

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

6.2.1 Results of the EAG preferred base-case scenario

Table 6.2 shows the results of the deterministic EAG's base-case (discounted and using the [redacted] price for ruxolitinib and list prices for BAT). These indicate that ruxolitinib is more costly but also more effective than BAT, accruing [redacted] incremental QALYs at [redacted] additional costs, resulting in an ICER of £20,987 per QALY gained. When accounting for disease severity, considering a QALY weight of 1.2, incremental QALYs are now [redacted], which results in an ICER of £17,489 per QALY gained.

Compared to the company's base-case after clarification shown in Table 5.2, the incremental costs were reduced by [redacted], whereas the incremental QALYs were reduced by [redacted]. This is due to 1) increasing the number of QALYs in all health states (except relapse) for BAT and decreasing in all health states for ruxolitinib, and 2) extending life years in BAT is associated with increasing subsequent treatment, cGvHD treatment and management costs, whereas the opposite occurred for ruxolitinib. This can be seen by comparing Tables 6.3 and 6.4 to Tables 5.3 and 5.4, where disaggregated discounted QALYs and costs, respectively, are shown. Overall, the reduction in incremental costs is larger than the reduction in incremental QALYs, causing the EAG base-case ICER being lower than the company's base-case ICER.

Table 6.2: EAG base-case CE results (deterministic), with [redacted] price

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)	ICER with severity modifier (£/QALY)
BAT	83,878	2.73	1.39	–	–	–	–	–
Ruxolitinib	[redacted]	3.47	[redacted]	[redacted]	0.74	[redacted]	20,987	17,489

Based on updated economic model, following the clarification phase[1]
BAT = best available therapy; [redacted] CE = cost effectiveness; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; Inc. = incremental; LYG = life years gained; QALY = quality-adjusted life years

Table 6.3: Disaggregated QALYs results (discounted)

Health state	QALY BAT	QALY Ruxolitinib	Increment vs. BAT	Absolute increment	(%) Absolute increment
Failure-free	0.22	[redacted]	[redacted]	[redacted]	[redacted]
New systemic treatment	0.12	[redacted]	[redacted]	[redacted]	[redacted]
Relapse	0.05	[redacted]	[redacted]	[redacted]	[redacted]
cGvHD, failure-free	0.36	[redacted]	[redacted]	[redacted]	[redacted]
cGvHD, new systemic treatment	0.59	[redacted]	[redacted]	[redacted]	[redacted]
cGvHD, relapse	0.05	[redacted]	[redacted]	[redacted]	[redacted]
IV disutility	0.00	[redacted]	[redacted]	[redacted]	[redacted]
AE disutility	-0.01	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs	1.39	[redacted]	[redacted]	[redacted]	[redacted]

Based on updated economic model, following the clarification phase[1]
AE = adverse events; BAT = best available therapy; cGvHD = chronic graft-versus-host disease; IV = intravenous; QALY = quality-adjusted life years

Table 6.4: Disaggregated cost results (discounted), with [redacted] price

Cost item	Cost BAT (£)	Cost Ruxolitinib (£)	Increment vs. BAT (£)	Absolute increment (£)	(%) Absolute increment
Drug acquisition cost	9,352	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment cost	3,125	[redacted]	[redacted]	[redacted]	[redacted]
cGvHD treatment cost	15,525	[redacted]	[redacted]	[redacted]	[redacted]
Administration cost	0	[redacted]	[redacted]	[redacted]	[redacted]
Disease management cost	54,666	[redacted]	[redacted]	[redacted]	[redacted]
AE cost	1,209	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	83,878	[redacted]	[redacted]	[redacted]	[redacted]

Based on updated economic model, following the clarification phase[1]
AE = adverse events; BAT = best available therapy; [redacted]; cGvHD = chronic graft-versus-host disease

In Figure 6.1, the OS as observed from the modelled EAG base-case is compared to the OS as observed in REACH2. It appears that the curves separate slightly earlier in the model, and visually it appears that the area between the curves is slightly larger for the modelled survival, but overall, the combination of all time to event curves used in the model appears to reflect the observed OS quite well up to 24 months. The slightly larger area between the curve likely reflects the correction to the BAT survival for patients crossing over to ruxolitinib.

Figure 6.1: Observed OS in EAG's base-case versus OS REACH2

Based on updated economic model, following the clarification phase[1]
BID = twice daily; EAG = Evidence Assessment Group; OS = overall survival

6.2.2 Results of the EAG PSA, DSA and company scenarios

Table 6.5 shows the results of the probabilistic EAG's base-case (discounted and using the [redacted] price for ruxolitinib and list prices for BAT). These indicated that ruxolitinib was more costly but also more effective than BAT, resulting in an ICER of £20,659 per QALY gained. When accounting for disease severity, considering a QALY weight of 1.2, incremental QALYs were now [redacted], which results in an ICER of £17,216 per QALY gained.

These EAG's PSA results are comparable with the EAG base-case results. The CE-plane presented in Figure 6.2 shows that [redacted]. This indicates that ruxolitinib is likely to be [redacted] compared to BAT. Based on the CEAC shown in Figure 6.3, the probability that ruxolitinib is cost effective at thresholds of £20,000 and £30,000 per QALY gained when severity weighting is applied is [redacted] and [redacted], respectively. If no severity weighting is applied, the probability is [redacted] and [redacted], respectively.

Table 6.5: EAG base-case deterministic and EAG base-case PSA results (discounted), with [redacted] price

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
EAG base-case deterministic					
BAT	£83,878	1.39			
Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	20,987
EAG PSA					
BAT	£82,881	1.37			
Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	20,659

Based on updated economic model, following the clarification phase[1]
BAT = best available therapy; [redacted] EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life years

Figure 6.2: EAG probabilistic CE-plane

[redacted]

Based on updated economic model, following the clarification phase[1]
CE = cost effectiveness; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness; QALY = quality-adjusted life year

Figure 6.3: EAG probabilistic CEAC (ruxolitinib [redacted] price)

Based on updated economic model, following the clarification phase[1]
BAT = best available therapy; CEAC = cost effectiveness acceptability curve; EAG = Evidence Assessment Group; WTP = willingness-to-pay

The tornado diagram in Figure 6.4 shows the ten most influential parameters of the deterministic sensitivity analysis. The medical resource use has the largest impact on the ICER, but the impact is relatively modest.

Figure 6.4: DSA tornado diagram for EAG base-case (ruxolitinib, [redacted] price, without severity modifier)

Based on updated economic model, following the clarification phase[1]
BAT = best available therapy; [redacted] cGvHD = chronic graft-versus-host disease; DSA = deterministic sensitivity analysis; EAG = Evidence Assessment Group; FF = failure-free; HS = health state; ICER = incremental cost-effectiveness ratio; MRU = medical resource use; NST = new systemic therapy; TA = Technology Appraisal

The EAG also explored the impact of the company scenarios on the EAG base-case, these are presented in Table 6.6. The highest ICER for this scenario set was £30,022 (£25,018 with severity weighting),

when for all FF-state transitions joined models were assumed, with the choice of the parametric shape based on clinical input.

Table 6.6 : Summary of company defined scenario analyses applied to EAG base-case (ruxolitinib [redacted] price)

Description Scenario	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	ICER (£/QALY) with severity modifier
EAG base-case	[redacted]	[redacted]	20,987	17,489
Decision problem				
Time horizon = 20 years	[redacted]	[redacted]	20,318	16,9324
No discounting	[redacted]	[redacted]	24,218	20,182
Clinical data				
Transition probabilities from the naïve analysis	[redacted]	[redacted]	22,859	19,049
Best fitting models based on AIC/BIC	[redacted]	[redacted]	27,476	22,896
Individual models for all FF-state transitions; changed extrapolation options based on statistical fit (remaining transitions per base-case)	[redacted]	[redacted]	22,370	18,642
Individual models for all FF-state transitions; changed extrapolation options based on clinical input (remaining transitions per base-case)	[redacted]	[redacted]	27,656	23,047
Joint models for all FF-state transitions; changed extrapolation options based on statistical fit (remaining transitions per base-case)	[redacted]	[redacted]	24,103	20,086
Joint models for all FF-state transitions; changed extrapolation options were selected clinical input (remaining transitions per base-case)	[redacted]	[redacted]	30,022	25,018
Joint models for post-failure outcomes	[redacted]	[redacted]	24,192	20,160
Treatment waning after Year 3	[redacted]	[redacted]	20,987	17,489
Utilities				
Average observed utility values	[redacted]	[redacted]	19,751	17,489
Mixed effects model	[redacted]	[redacted]	22,653	18,878
Mixed effects model, without relapse	[redacted]	[redacted]	22,740	18,950
Fixed effects model	[redacted]	[redacted]	20,802	17,335
cGvHD utility from TA949	[redacted]	[redacted]	22,103	18,419
Costs and resource use				
ECP only for BAT	[redacted]	[redacted]	8,682	7,235
BAT per clinician survey	[redacted]	[redacted]	16,097	13,414

Description Scenario	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	ICER (£/QALY) with severity modifier
ECP use 60%	[redacted]	[redacted]	17,770	14,808
ECP use 80%	[redacted]	[redacted]	13,226	11,022
BAT per REACH2	[redacted]	[redacted]	26,589	22,158
2L BAT = 1L BAT	[redacted]	[redacted]	17,939	14,939
No resource use costs	[redacted]	[redacted]	Dominant	Dominant
cGvHD scenarios				
No costs for cGvHD	[redacted]	[redacted]	Dominant	Dominant
No resource use for cGvHD	[redacted]	[redacted]	3,353	2,795
BEL for 65% of 3L cGvHD	[redacted]	[redacted]	22,849	19,040
BEL only for 3L cGvHD	[redacted]	[redacted]	23,414	19,512

Based on updated economic model, following the clarification phase[1]

1L = first-line; 2L = second-line; 3L = third-line; AIC = Akaike Information Criterion; BAT = best available therapy; BEL = belumosudil; BIC = Bayesian Information Criterion; [redacted]; cGvHD = chronic graft-versus-host disease; EAG = Evidence Assessment Group; ECP = extracorporeal photopheresis; FF = failure-free; ICER = incremental cost-effectiveness ratio; Inc. = incremental; QALY = quality-adjusted life year; TA = Technology Appraisal

6.2.3 Results of the EAG additional exploratory scenario analyses

The results of the EAG scenario analyses are provided in Table 6.7. These results are all conditional on the EAG base-case settings. The scenario analyses conducted by the EAG indicated that the results were reasonably stable for the alternative assumptions explored. In the set of scenarios explored here, the results were most influenced by the estimated cost of BAT, though all ICERs remained well below £30,000, and in general the severity weighted ICER were close to £20,000.

Table 6.7: Results of exploratory scenario analyses by the EAG (discounted), with [redacted] price

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	ICER (£/QALY) with severity modifier
EAG base-case	[redacted]	[redacted]	20,987	17,489
Scenario analyses set 1: derivation and implementation of HRQoL in the model				
aGvHD FF long-term health state utility values higher than those of cGvHD patients	[redacted]	[redacted]	23,083	19,235
Equal utility value for acute and chronic GvHD NST health states	[redacted]	[redacted]	23,345	19,454
Separate statistical models for the utility values for aGvHD (REACH2) and cGvHD (REACH3) – Model 1	[redacted]	[redacted]	22,999	19,116
Separate statistical models for the utility values for aGvHD (REACH2) and cGvHD (REACH3) – Model 2	[redacted]	[redacted]	23,078	19,232
Separate statistical models for the utility values for aGvHD (REACH2) and cGvHD (REACH3) – Model 3	[redacted]	[redacted]	20,780	17,317
Separate statistical models for the utility values for aGvHD (REACH2) and cGvHD (REACH3) – Model 4	[redacted]	[redacted]	20,963	17,469
CADTH utility for responders after 12 weeks	[redacted]	[redacted]	22,708	18,923
Scenario analyses set 2: resource use and costs				
ECP only for BAT	[redacted]	[redacted]	8,682	7,235
Reduce overall BAT costs with 25%	[redacted]	[redacted]	26,767	22,306
Increase overall BAT costs with 25%	[redacted]	[redacted]	15,206	12,672
Hospitalisation rate based on crude data ([redacted])	[redacted]	[redacted]	24,190	20,158
Costs MSC £20,000	[redacted]	[redacted]	19,247	16,039

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	ICER (£/QALY) with severity modifier
Based on updated economic model, following the clarification phase[1] aGvHD = acute graft-versus-host disease; BAT = best available therapy; [redacted]; CADTH = Canadian Agency for Drugs and Technologies in Health; cGvHD = chronic graft-versus-host disease; EAG = Evidence Assessment Group; ECP = extracorporeal photopheresis; FF = failure-free; HRQoL =health-related quality of life; ICER = incremental cost-effectiveness ratio; MSC = mesenchymal stromal cells; NST = new systemic therapy; QALY = quality-adjusted life year; TA = Technology Appraisal				

6.3 EAG's preferred assumptions

The step-by-step changes made by the EAG to derive its base-case, using the CS base-case and the model submitted after clarification as starting point, can be seen in Table 6.8. The change with the largest impact on the results was the assumption that time from failure-free to relapse and to death would be the same for both treatments. This change led to a substantially lower ICER; though the incremental QALYs decrease as patients in BAT live slightly longer and in ruxolitinib slightly shorter, the incremental costs also decrease. Correcting the indexed cost of rehospitalisation increases the incremental costs and ICER slightly, whilst the impact of the other changes made by the EAG was negligible.

Table 6.8: Individual impact of EAG preferred assumptions

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	ICER severity weighted (£/QALY)
CS base-case						
BAT	79,632	1.37	–			
Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	33,133	27,611
CS base-case after the clarification						
BAT	79,292	1.32	–			
Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	30,193	25,161
Correction of errors on sheet 'Survival data' (1)						
BAT	79,292	1.32				
Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	26,235	21,862
(1) + Correction error indexing cost rehospitalisation						
BAT	80,521	1.32	-	-		
Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	27,243	22,703
(1) + Ruxolitinib only different time to NST						
BAT	82,580	1.39	-	-		
Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	19,960	16,633
(1) + Utility cGvHD ≤ 4 cycles equal to failure-free <= 4 cycles						
BAT	79,292	1.31	-	-		
Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	26,229	21,858

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	ICER severity weighted (£/QALY)
(1) + Disutility AE multiplicative						
BAT	79,292	1.32	-	-		
Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	26,214	21,845
All changes combined (EAG base-case)						
BAT	83,878	1.39	-	-		
Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	20,987	17,489

Based on updated economic model, following the clarification phase[1]
AE = adverse event; BAT = best available therapy; cGvHD = chronic graft-versus-host disease; CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; NST = new systemic therapy; QALY = quality-adjusted life year

6.4 Conclusions of the cost effectiveness section

The CS[3] and response to clarification[5] provided sufficient details for the EAG to appraise the literature searches conducted to identify relevant clinical evidence on cost effectiveness, HRQoL and cost/health care resource use in patients with aGvHD or cGvHD. Searches were conducted in July 2019, with updates in September 2021 and January 2024. Searches were transparent and reproducible, and comprehensive strategies were used. Bibliographic databases, HTA Agency websites, conference proceedings and trials registers were searched. Overall, the EAG has no major concerns about the literature searches conducted.

The company's base-case complied with the NICE reference case. A potential equity issue was raised by the company in the CS, where it is mentioned that ECP availability is limited to five therapeutic apheresis services units in England and that travel time increases the risk of infections. The eligibility for ECP also depends on patients having a good venous access and being haematologically stable. Currently, some centres in England use their own budget to enable patient access to ruxolitinib. Some patients self-fund or use private healthcare to access ruxolitinib, which creates inequity in patients with GvHD across England. In Wales and Scotland, patients already have access to ruxolitinib, which creates inequity of access across the UK.

The key issues highlighted by the EAG throughout this report (and summarised in Table 6.1) were the following:

1) The EAG considers that the likely mixture of patients (in terms of treatment response and/or resolution of symptoms) in the FF health states is not completely captured in the model.
2) The EAG is uncertain about the modelling of patients with chronic disease since the chronic population in the model and the population in REACH3 do not completely align.
3) The EAG does not agree (in general) with the choices made by the company to extrapolate (FF) survival data.
4) The EAG is uncertain about the implementation of health state utilities (some of the health state utility values and some modelling assumptions).

The first concern of the EAG in this submission regarding the CE evidence was related to a potential mixture of patients in the FF health states. Since response to treatment is not implicitly included in the model, the FF health state includes a mixture of patients who are still experiencing aGvHD symptoms

and those that are in remission after treatment response. These two subgroups of patients who are likely to experience very different survival and QoL outcomes. It seems likely that this mixture changes over time, as those who continue to experience aGvHD symptoms will probably transition to another treatment (NST). This distinction is expected to be relevant for patients who transition from FF aGvHD to another health state (e.g., patients in FF transitioning to cGvHD (FF) for whom their aGvHD symptoms are not yet resolved would presumably have worse survival and QoL outcomes than those in FF in remission after treatment response transitioning to cGvHD).

Another EAG concern is related to the modelling of patients in the chronic health state (cGvHD). There seems to be a mismatch between the chronic population intended to be modelled and the population in REACH3, since in REACH3 only 10.4% of patients had SR-aGvHD, whereas the model assumes 100%. It is also unclear whether for these patients in REACH 3 the symptoms of aGvHD were resolved or not. Chronic patients that have aGvHD symptoms not resolved may be quite a different population than the chronic patients who have the acute disease resolved.

Also, the EAG is concerned that the choice between ECP and the other treatments might be driven by clinical characteristics, implying that subgroup analysis should be used with the comparator varying by subgroup, with one being ECP. The cost effectiveness of these subgroups, if relevant, should be then analysed separately. In the current version of the model, it is possible to make changes to the proportion of patients receiving ECP, but this only affects the estimated total costs. In a subgroup analysis, patients characteristics and clinical effectiveness should match those in the subgroup. This, however, cannot be changed in the current model. If ECP alone is more effective than BAT, the incremental QALYs should decrease. But if life is also extended for ECP patients, which might be the case based on Figure 9 in the clarification letter response (HR: 1.118, p=0.639),[5] the total costs of the ECP arm could increase as well. Therefore, it is uncertain if for this subgroup the ICER will increase or not.

In general, the company's approach to survival data extrapolation seems to lack consistency, which in some cases results in implausible and/or contradictory decisions. Some examples of this are summarised below:

- The company indicated that '*model validation was undertaken using the individual models fit to the BAT data as the patterns of survival for BAT with each curve are comparable between the individual and joint models, and the choice of curves is not affected by the switch to joint models*'.[3] It should be noted that it seems that experts did not validate the predictions for the ruxolitinib arm. The EAG considers that it would have been better to show the ruxolitinib curves to the experts as well.
- The low number of patients at risk after 3 months (as can be seen in Figure 4.2) suggests that there is high uncertainty associated to the survival data estimates and their long-term extrapolations.
- The validity of crossing survival data (not only the extrapolations) is unclear.
- The company assumed joint models for the transitions from FF to relapse and death, since separate individual models would not provide clinically plausible extrapolations due to the crossing of the ruxolitinib and BAT curves. This crossing however is not observed only in the extrapolations but in the KM data as well. Therefore, if the validity of the extrapolations is questioned, the validity of the REACH2 data should also be questioned.
- Likewise, the company indicated that due to the censoring of competing events, it was not considered plausible to assume that the risk of failure or relapse would be higher with ruxolitinib compared with BAT, but again, this is what REACH2 data shows. For the transition from FF to relapse, the KM shows that both curves seem to converge and that there is no

separation after 2 years. Assuming a PH model (see Figure 20 in CS) implies an immediate initial and continued benefit for ruxolitinib that does not appear to be supported by the observed data.

- The company's estimation of the transition from FF to death seems incorrect since the KM curve for BAT is higher than the KM for ruxolitinib, but the opposite is seen in the extrapolated curves.
- The selection of independent or PH extrapolation models is also problematic. The company refers to a global test to support PH models, but it is unclear what test is referred to. Based on Figure 4.2 and log-log plots in CS (Figure 18),[3] the EAG considers that the PH assumption is only plausible for time to NST. For other transitions, crossing curves and/or delayed separation is observed, which are not possible under PH.
- For the transition from failure-free to cGvHD, the company stated that independent models were selected irrespective of the crossing of the log-log curves to reflect the observed incidence of events within REACH2 after accounting for competing risks. The EAG wonders why the same argument was not valid for FFS (acute) transitions where there is also crossing of survival curves (Figure 4.2).
- Regarding the selection of the preferred extrapolation curves, the company explained that clinical experts preferred the Gompertz and gamma models, but the company selected the generalised gamma based on the best statistical fit. As shown in Figure 20 of the CS,[3] the fit to the data seems to be poor in any case, meaning that there is uncertainty about the values used for these transitions in the model.
- In response to Clarification Question B1c,[5] the company contacted clinical experts who indicated that they did not expect the incidence of cGvHD to be different between BAT and ruxolitinib (after accounting for the competing events). Based on this, their base-case was updated and the same rate of cGvHD was assumed for both arms, which was estimated from the pooled ruxolitinib and BAT data in REACH2.

Based on the issues listed above, the EAG considered that a simple way to overcome some of them could be adopting a pragmatic approach where the only benefit of ruxolitinib over BAT would be on delaying time to NST. For the other transitions, acknowledging the outstanding uncertainties, these could be considered equal between both arms. This represents the EAG's preferred approach used to define the EAG base-case.

In terms of HRQoL, the EAG is concerned about the appropriateness of pooling the data from REACH2 and REACH3 to fit a single statistical model to estimate HSUVs because these trials include different patient and disease populations. The choice of the company's preferred statistical model to estimate utilities seems to be based upon clinical expert opinion only, while statistical goodness-of-fit should have been used as well. Finally, the estimated utility values for some health states might lack face validity. Special attention is required for patients with chronic disease for whom acute symptoms are not resolved.

The EAG agreed in general with the company in the approach taken to model resource use and costs. There were several minor issues detected which did not (or are not expected to) have a significant influence on the model results, which are listed below:

- Drug acquisition costs are based upon costs per mg (obtained from cost per pack and pack size), while NICE recommends the use of costs per pack. Unfortunately, the EAG cannot adequately correct for this, because crucial information is missing such as the percentage of patients

receiving treatment in the hospital over time (where packages are likely to be shared) and the number of weeks dispensed at a time.

- The company did not include the costs of steroids based on the observation in the REACH2 trial that these were approximately the same for both groups. In general, when there is a difference in mortality between treatment groups, omitting costs that occur in both groups can lead to an over- or underestimation of the ICER. However, in this case, the difference in mortality is small, and the costs associated with steroid use will be low.
- The approach of the company to estimate the drug acquisition costs implicitly includes the tapering of treatment and dose reductions due to safety reasons. Because of this approach, it is not feasible to explore the impact of different tapering strategies.
- There appears to be an error in the company's estimation of the number of hospital admissions per 4-week cycle: [redacted]/267 = [redacted] per patient year and [redacted] per 4-week cycle, rather than the [redacted] per 4-week cycle reported in the company submission. It is unclear to the EAG what the source is of the discrepancy, and thus it is also not clear which of these values is correct.
- The company applied PPSRU inflation rates to index the findings from Dignan et al. to current price levels.[44] The cost per readmission in Dignan is £10,091 which was inflated to £11,786. However, using the price year in Dignan of 2010, and indexing to 2023, the correct cost estimate is £13,342, which is substantially higher (see also footnote Section 4.2.9.4). Based on [redacted] readmissions per 4-week cycle, this yields a cost of £1,134.04 per cycle for readmissions. This corrected value was applied in the EAG base-case.
- The costs taken from Dignan et el. 2013[44] are not fully representative for the readmission costs for the aGvHD patients in the decision model. The costs in Dignan et al. also include costs of admission due to relapse of the underlying disease, while these relapse treatment costs are separately included in the model. Furthermore, Dignan et al. included a smaller proportion of patients with grade III/IV aGvHD (32% compared to 65% in REACH2 trial),[44] and report that patients with more severe aGvHD have higher readmission costs. Given the information provided by Dignan et al. 2013,[44] it is possible to correct for the different case-mix, leading to higher readmission costs. However, based on the data provided it is not possible to adjust the readmission costs for the inclusion of the relapse costs, but such correction would decrease the readmission cost estimate. Overall, the EAG agrees with the use of the costs as used by the company (but with the correction inflation rate) under the assumption that the underestimation of the costs due to the different case-mix is balanced out by the overestimation of the costs due to the inclusion of relapse readmission costs.
- The costs of relapse for AML were included for all relapsed treatments, while only 39% of the patients had AML as underlying disease. The EAG considers that it is not possible to provide a better estimate of these costs, due to the lack of evidence about relapse treatment costs for the other underlying diseases. Although these costs might differ for other malignancies, the EAG expects that it would not have a substantial impact on the ICER as there will not be difference in the probability of relapse between the treatment arms in the EAG base-case.

The company's base-case deterministic CE results (discounted and using the [redacted] price for ruxolitinib and reference list prices for BAT) for ruxolitinib compared to BAT indicated that ruxolitinib has higher associated costs and QALYs compared to BAT, resulting in [redacted] incremental QALYs and a total cost increase of [redacted]. Using the [redacted] price for ruxolitinib and reference list prices for BAT, the ICER for ruxolitinib compared with BAT was £30,193 per QALY gained. When accounting for disease severity, considering a QALY weight of 1.2, the resulting ICER was £25,161per QALY gained. The average PSA results were in line with the deterministic ones. The plot of the PSA outcomes on the CE-plane

indicated that [redacted]. The CEAC plot indicated that ruxolitinib was dominant in [redacted] of the simulations and was cost effective in [redacted] and [redacted] of the simulations at the common willingness-to-pay (WTP) thresholds of £20,000 and £30,000 per QALY gained, respectively. The company's DSAs indicated that most input parameters had a minor impact on the model results, except for the health state costs and the utility values used the model. Nevertheless, changes in ICER were relatively modest. Similarly, the scenario analyses explored by the company suggested that only the scenarios where different GvHD resource use/costs were not included in the scenarios resulted in very low ICERs. On the opposite direction, the only scenario resulting in an ICER above the common thresholds used by NICE was the one where a shorter time horizon of 20 years was assumed. Scenarios where the BAT distribution is changed should also impact QALYs, since some of the options included in BAT seem to be more effective than others. However, this is not possible in the model, where changes in the BAT distribution only affects costs.

The EAG defined a new preferred base-case by making the following changes (as listed in Section 6.1.1):

1. Correcting some errors found on the "Survival Data" sheet of the model, where for all transitions starting from NST and relapse, selecting the joint distribution led to a different constant for the gamma distribution for BAT and ruxolitinib.
2. On the "Control" sheet of the model, the pooled distributions starting from FF were not included, which means that when these curves are selected, the PSA does not incorporate the associated uncertainty. The EAG added the coefficients of these pooled curves to the PSA.
3. The company applied PPSRU inflation rates to index the cost per readmission from Dignan et al. to current price levels.[44] The cost from Dignan is £10,091 which was inflated to £11,786. However, using the price year in Dignan of 2010, and indexing to 2023, the correct indexed costs are £13,342, which is substantially higher. Based on [redacted] readmissions per 4-week cycle, this yields a cost of £1,134.04 per cycle for readmissions. The revised cost estimate is also used for the proportion of patients that are in hospital at the start of the model.
4. The company used an additive approach to disutilities whereas the NICE methods guide states a preference for a multiplicative approach. Thus, the latter is selected for the EAG base-case.[37]
5. The company's approach to survival data extrapolation lacks consistency, which in some cases results in implausible and/or contradictory decisions. The EAG adopted a pragmatic approach where the only benefit of ruxolitinib over BAT would be on delaying time to NST. For the other transitions, acknowledging the outstanding uncertainties, the EAG has made the assumption that they can be considered equal between both arms
6. The EAG has some reservations about the utility associated with the cGvHD health state ([redacted]) compared to the utility for the first four cycles in failure-free aGvHD ([redacted]). When patients remain FF for some time (for example, four model cycles) it is reasonable to assume they experience an increase in utility over time. It could be assumed that for these patients, who still are in FF, the symptoms of aGvHD have been resolved and, therefore, transitioning to cGvHD (for example, after four model cycles) might not be associated with a substantial difference in QoL, though an initial decrease in utility would be more plausible. However, the main concern of the EAG relates to the substantial increase in QoL for patients who transition from FF aGvHD to cGvHD within the first four model cycles. Following the previous rationale, it could be assumed that these patients are still experiencing symptoms of aGvHD when

transitioning to cGvHD. The EAG considers that a large improvement in the utility value for these patients seems irrational given that these patients are expected to be much sicker, the treatment has not really changed, and response has not been achieved. The EAG, therefore, prefers using a lower utility value for patients in the cGvHD states during the first four model cycles. This utility should at most be equal to the utility for aGvHD in the first four cycles, though it could be argued that these patients might experience even lower HRQoL due to experiencing symptoms of both acute and chronic disease. To address some of the EAGs reservations about the utility values for cGvHD health states, in the first four model cycles the FF cGvHD utility is assumed to be equal to the utility value in the FF aGvHD health state.

The results of the EAG's base-case analysis indicated that ruxolitinib was more costly but also more effective than BAT, accruing [redacted] incremental QALYs at [redacted] additional costs, with an ICER of £20,987 per QALY gained. When accounting for disease severity, considering a QALY weight of 1.2, incremental QALYs were now [redacted], and the ICER was £17,489 per QALY gained. Compared to the company's base-case after clarification shown in Table 5.2, the incremental costs were reduced by [redacted], whereas the incremental QALYs were reduced by [redacted]. This is due to 1) increasing the number of QALYs in all health states (except relapse) for BAT and decreasing in all health states for ruxolitinib, and 2) extending life years in BAT is associated with increasing subsequent treatment, cGvHD treatment and management costs, whereas the opposite occurred for ruxolitinib. Overall, the reduction in incremental costs is larger than the reduction in incremental QALYs, causing the EAG base-case ICER to be lower than the company's base-case ICER. The EAG's average PSA results were comparable with the EAG base-case results. The PSA ICER was £20,659 per QALY gained. The plot of the PSA outcomes on the CE-plane showed that [redacted]. This indicates that ruxolitinib is likely to be [redacted] compared to BAT. The CEAC estimated the probability that ruxolitinib is cost effective at thresholds of £20,000 and £30,000 per QALY gained at [redacted] and [redacted], respectively, when a severity weight is applied. If no weighting is applied, the probabilities are [redacted] and [redacted], respectively. The scenario analyses conducted by the EAG (both those defined by the company as the additional EAG exploratory scenarios) indicated that the results were reasonably stable for the alternative assumptions explored. The highest ICER was £30,022 (£25,018 with severity weighting), when for all transitions from FF joined models were assumed, with the choice of the parametric shape based on clinical input.

In general, ruxolitinib seems to be more costly but also more effective than BAT. Most of the ICERs obtained in different scenarios are in the range £20,000 and £30,000 per QALY gained, including the EAG base-case. However, as highlighted in Table 6.1, there are several uncertainties present in the analyses that cannot be resolved at this moment such as the mixture of patients in FF and the modelling of the chronic population. It is unclear what the impact of these uncertainties may be on the cost effectiveness results.

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Appendix 1: Questions to and responses from clinical experts

Dr Andrew Gunnery

Professor/Honorary consultant in Paediatric Immunology + HSCT

Institute of Translational and Clinical Research

Paediatric Immunology Dept

c/o Ward 3

Q1. Could you explain if patients with acute GvHD (aGvHD) can have their acute condition resolved and then develop (or be categorized as) chronic GvHD (cGvHD), and also if they can develop the chronic condition with the acute condition not resolved?

Yes, yes and yes. You can have acute which resolves, then develop chronic, you can develop chronic never having has acute, and you can have mixed with acute and chronic.

Q2. When would aGvHD patients be expected to transform into cGvHD once aGvHD is resolved from a clinical point of view (the conditions under which this occurs) and in terms of time?

Difficult to say, in view of above. Classically aGvHD is ,100 days post HSCT, with appropriate clinical features, and cGvHD is >100 days post HSCT, with appropriate clinical features, but aGvHD could occur after 100 days, and overlap syndrome (with both features) could be before or after 100 days.

Q3. Could you please explain if the clinical profile of patients with cGvHD that come via the aGvHD once aGvHD is resolved would be different from that of patients that experience directly cGvHD after allogeneic stem cell transplant (alloSCT) i.e. chronic GvHD direct from alloSCT?

No, not different.

Q4. Could you please explain if the treatment pathway of patients with cGvHD that come via the aGvHD once aGvHD is resolved would be different from that of patients that experience directly cGvHD after alloSCT?

Depends on the centre, but not really different. Belumosudil is available for cGvHD, but not aGvHD – so that is different.

Q5. Related to their health-related quality of life status:

a. Would you expect the quality of life for aGvHD patients that transform into cGvHD once aGvHD is resolved to experience an increase/decrease? Would you expect this change (increase/decrease) to be relatively large and why?

Neither are great – probably not a lot of difference

b. Would you expect the quality of life for aGvHD patients that require a second/third line of systemic therapy to be different than for cGvHD patients once aGvHD is resolved that require a second/third line of systemic therapy?

Probably not a lot of difference

c. Would aGvHD patients remaining in a failure-free state (i.e. no need for another systemic therapy/no relapse/no death/no development of cGvHD) be expected to have comparable quality of life to patients to patients with cGvHD once aGvHD is resolved or would cGvHD patients once aGvHD is resolved be expected to have a higher degree of comorbidities and be sicker, and have therefore a worse quality of life?

Once aGvHD is resolved, patients should be normal, unless they have chronic organ damage (e.g., liver dysfunction, or bowel stenosis), so overall a resolved aGvHD patient should have a better quality of life than one with on-going cGvHD.

Q6. Would the overall survival of patients in the cGvHD health state once aGvHD is resolved be expected to be worse, better or similar to the overall survival of aGvHD patients?

It would be similar – because you die of aGvHD, or get better, whereas with cGvHD, it may resolve, remain as a chronic disability, or you may die of complications related to disease or treatment.

Q7. How do you treat patients with steroid refractory aGvHD?

a. What percentage of patients would receive extracorporeal photopheresis (ECP)?

In our centre – all would be considered for ECP.

b. What patient characteristics would make ECP unsuitable?

Permanently unsuitable - Difficult venous access, sensitivity to the photoactive ingredient (Psoralen). Temporarily unsuitable – sepsis, unstable blood pressure

c. What percentage of patients who are suitable for ECP cannot access it?

At our centre, virtually none, but nationally it will be some – patients who do not have easy geographic access for instance – not sure I can put a figure on it.

d. Are there any patients who you would prefer to not treat with ECP? Which treatments would you use instead with approximate percentages?

Not in our paediatric centre – possibly in adult centres, but I do not have figures

Q8. How do you treat patients with cGvHD, with approximate percentages?

We prefer ECP, but there are patients with aGvHD and cGvHD where you may be looking for a rapid response, and ECP takes several weeks (2-3 at least) to show a response – so 90% + of ours would get ECP (but will likely also be receiving other treatment e.g., steroid, infliximab, MMF, CNI but possibly mTOR inhibitor or ROCK2 inhibitor)

Dr Francesca Kinsella

Consultant Haematologist

Director of the Birmingham Centre for Cellular Therapy and Transplantation

Honorary Senior Lecturer Institute of Immunology and Immunotherapy

Birmingham ECMC Immunotherapy Lead

Q1. Could you explain if patients with acute GvHD (aGvHD) can have their acute condition resolved and then develop (or be categorized as) chronic GvHD (cGvHD), and also if they can develop the chronic condition with the acute condition not resolved?

Acute GvHD is defined according to criteria set out by the Mount Sinai Acute GvHD International Consortium (MAGIC) group (Harris et al BBMT 2016). Diagnosis of chronic is according to the NIH consensus criteria. The following apply:

- *Classic aGvHD occurs within 100 days of allo-SCT with features of aGvHD but with no diagnostic or distinctive features of cGvHD.*
- *Persistent / recurrent / late onset aGvHD occurs beyond 100 days post allo-SCT, but with features of aGvHD and no diagnostic or distinctive features of cGvHD.*
- *Classic cGvHD can occur at any time point post allo-SCT with diagnostic or distinctive clinical features of cGvHD, and none of aGvHD.*
- *Overlap syndrome can occur anytime post allo-SCT, with features of both acute and chronic GvHD.*

Therefore as you can see patients may just have acute GvHD, and then may develop de novo chronic GvhD, but can develop chronic features on top, in which instance it is termed 'overlap' GvHD.

Q2. When would aGvHD patients be expected to transform into cGvHD once aGvHD is resolved from a clinical point of view (the conditions under which this occurs) and in terms of time?

The phrasing and concept of this question is misinformed I'm afraid. Development of chronic GvHD is not guaranteed following acute GvHD. However, patients with acute GvHD are at higher risk of developing chronic GvHD. As per the definitions above, timeframe alone is not a diagnostic criteria for GvHD, but the majority of acute GvHD will present within the first 3 months, whilst the majority of chronic cases occur at an average of 6-9 months post allo-SCT.

Q3. Could you please explain if the clinical profile of patients with cGvHD that come via the aGvHD once aGvHD is resolved would be different from that of patients that experience directly cGvHD after allogeneic stem cell transplant (alloSCT) i.e. chronic GvHD direct from alloSCT?

Chronic GvHD is a clinical diagnosis. There is significant heterogeneity between patients because of the variety of organs involved. The same NIH consensus criteria are used to assess both sets of patients as they have the same spectrum of possible GvHD involvement. There is no data to say definitively that patients who suffer acute and subsequent chronic GVHD have different patterns of disease, but it is clear that patients with overlap GvhD, or those who rapidly develop severe chronic GvhD following acute GvhD have a poorer prognosis and higher TRM at 1 year.

Q4. Could you please explain if the treatment pathway of patients with cGvHD that come via the aGvHD once aGvHD is resolved would be different from that of patients that experience directly cGvHD after alloSCT?

There is currently no difference to the treatment pathway for either group of patients.

Q5. Related to their health-related quality of life status:

a. Would you expect the quality of life for aGvHD patients that transform into cGvHD once aGvHD is resolved to experience an increase/decrease? Would you expect this change (increase/decrease) to be relatively large and why?

Chronic GvHD is always associated with a reduction in QoL and increase in health care usage irrespective of how it arises.

Rather than QoL being associated to prior acute GvHD, it is significantly associated with severity of chronic GvHD. Overlap GvHD is frequently omitted from studies but one would expect these patients to have a significantly reduced QoL as well.

b. Would you expect the quality of life for aGvHD patients that require a second/third line of systemic therapy to be different than for cGvHD patients once aGvHD is resolved that require a second/third line of systemic therapy?

The severity of chronic GvHD significantly impacts upon QoL at 2nd/3rd line therapy in both scenarios. There are many factors to consider when appraising the domains that contribute to QoL: Physical, Sexual, Psychological, Societal, and I'm not sure an analysis will ever demonstrate an independent association between prior resolved acute Gvhd and QoL in latter chronic GvhD at 2nd/3rd line treatment.

c. Would aGvHD patients remaining in a failure-free state (i.e. no need for another systemic therapy/no relapse/no death/no development of cGvHD) be expected to have comparable quality of life to patients to patients with cGvHD once aGvHD is resolved or would cGvHD patients once aGvHD is resolved be expected to have a higher degree of comorbidities and be sicker, and have therefore a worse quality of life?

Patients who suffer acute GvHD that resolves will overall be expected to have a significantly better QoL, and decreased health care useage than patients who go on to develop chronic GvHD. This is true irrespective of whether the chronic GvHD patient had prior acute GvHD.

Q6. Would the overall survival of patients in the cGvHD health state once aGvHD is resolved be expected to be worse, better or similar to the overall survival of aGvHD patients?

I'm afraid this question is difficult to answer as you haven't qualified whether the comparator is the overall population of patients with acute GvHD or the population for whom it resolves without subsequent chronic GvHD.

If it's the latter then the OS of patients with chronic GvHD relates again to the severity of the chronic disease, rather than prior acute GvHD. Moderate and Severe chronic GvHD would certainly be associated with worsened OS compared to patients who previously had had acute GvHD and recovered with no subsequent chronic GvHD.

Q7. How do you treat patients with steroid refractory aGvHD?

a. What percentage of patients would receive extracorporeal photopheresis (ECP)?

The vast majority – 85-90% as we have it on site and it's commissioned and available to us.

b. What patient characteristics would make ECP unsuitable?

Cytopenia (HCT <0.27, plts <20), but this can generally be supported with transfusions. Blood borne viruses with reactivation, difficult IV access, multiple previous lines, patients for whom a rapid response is needed (e.g. grade 3-4 acute GvHD including gut and liver features.). Patients who live a considerable distance from the unit. Patient choice, Diarrhoea – as patients are connected to the ECP machine for 2-3 hours. apheresis nursing team capacity and competency to deliver the therapy.

c. What percentage of patients who are suitable for ECP cannot access it?

If we are going by the criteria above, then theoretically 0% of eligible and suitable patients cannot access it here at our unit, as it's delivered in house. Provision varies across England though with some centres depending upon NHSBT services (via SLA) to deliver ECP, and in that setting there may be a small rate of patients who cannot receive it.

In reality, there will always be individual logistical factors that may impede a patient attending for ECP (e.g. lives very far away, or limited apheresis team capacity).

d. Are there any patients who you would prefer to not treat with ECP? Which treatments would you use instead with approximate percentages?

The only situation in which I would consider ECP before other therapies would be for isolated acute skin GvHD up to grade 3 MAGIC (St III skin) ~10-15% patients. In all other situations (85-90%) now I would prefer Ruxolitinib 2nd line given the REACH 2 data and accumulating real world evidence.

In particular, patients with Steroid dependent or refractory lower gut or liver acute GvHD need rapid responses and I would particularly like to be able to access Ruxolitinib for these patients (by definition grade 2 or more).

All other therapeutic options will fall to 3rd line after ruxolitinib in my mind, unless there is no access for the drug to the proximal small bowel for absorption. In that situation our unit has more experience with infliximab

Isolated steroid refractory liver GvHD (<5% of all presentations) remains probably one of the more difficult presentations to treat though.

Q8. How do you treat patients with cGvHD, with approximate percentages?

As per current British guidelines (Dignan et al 2012 – being re-written – I am lead author), and EBMT guidelines where possible. Clinical trials are best for patients but in real world setting:

For moderate and severe chronic GvHD:

1st line – 1mg/kg pred +/- Ciclosporin

In setting of GvHD progression / steroid refractoriness / steroid dependency / steroid intolerance 2nd line treatment should be considered (generally within 3 months).

2nd line currently – ECP predominantly, rarely MMF (added in on top of first line to hopefully allow withdrawal as well as disease response). I WOULD WANT RUX AVAILABLE HERE 2ND LINE GIVEN REACH3 DATA.

3rd line - Belumosudil (now commissioned 3rd line)

4th line – anything not used 2nd/3rd line, or: ritux, imatinib, low dose MTX (never used), AIM IS FOR CLINICAL TRIALS.

Further clarification on Question 8. was sought in the following email:

Hi Francesca,

Thanks very much for your responses. I wonder if I might ask for some clarification regarding question Q7. How do you treat patients with steroid refractory aGvHD?

You say the following (*in italics*):

In response to part a. What percentage of patients would receive extracorporeal photopheresis (ECP)?

"The vast majority – 85-90% as we have it on site and it's commissioned and available to us."

In response to part d. Are there any patients who you would prefer to not treat with ECP? Which treatments would you use instead with approximate percentages?

The only situation in which I would consider ECP before other therapies would be for isolated acute skin GvHD up to grade 3 MAGIC (St III skin) ~10-15% patients. In all other situations (85-90%) now I would prefer Ruxolitinib 2nd line given the REACH 2 data and accumulating real world evidence.

Your first response suggests that standard clinical practice is to give the majority of patients ECM. However, your second response seems to suggest the opposite. You also state that you would prefer ruxolitinib 2nd line. Please bear in mind that we are considering a situation where ruxolitinib has not been recommended for steroid refractory aGvHD i.e. we need to know what you would give patients with steroid refractory aGvHD in a world without ruxolitinib in order to establish what ruxolitinib needs to be compared to for its evaluation.

Could you therefore reconsider your responses to questions Q7.a. and d. and/or provide some additional explanation for the responses you have given.

Many apologies if I have misunderstood anything and for any inconvenience. I am also happy to have Zoom or Teams call if you would find that helpful.

BW
Nigel
The response was in the following email:

Thanks Nigel,
In response to your question – in a world without rux, ECP would have to be the therapeutic option if deliverable.
If it isn't options can range (all unlicensed), and lack evidence. Different units have different experiences but we have used infliximab for steroid refractory acute GvHD of the gut, and once or twice, alemtuzumab for isolated liver steroid refractory GvHD.

BWs
Francesca

Single Technology Appraisal

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

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Thursday 19 September** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Inaccurate description of the company base-case, and lack of clarity regarding EAG's Key Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
The EAG inaccurately describe that the company base-case includes the analysis which is not adjusted for crossover – page 68	Please remove "Although the company performed an appropriate crossover adjustment, the unadjusted analysis formed the company base-case, and any bias favours BAT, thus producing a conservative estimate."	As described on page 92 of the company submission (CS), "Crossover may bias estimates of post-failure outcomes and therefore estimates of time to relapse, death and cGvHD have been adjusted in patients who crossed over. The two-stage method recommended in NICE DSU 16 was used to adjust survival times for crossover".	Corrected. An additional correction was also made on p.49. The EAG have added additional text in Sections 1 and 3.2 for clarification.
Additionally, Key Issue 3 as described by the EAG is unclear - page 11, 13-14	Please provide more detail around Key Issue 3, in particular around the following wording "However, given that death would preclude progression to cGvHD it seems likely that crossover also inflated the incidence of cGvHD, which means that ruxolitinib might have a worse effect in comparison to ECM in clinical practice than observed in the trial. This is, of course, made more uncertain by any mismatch between BAT and ECM. This is therefore a key issue."." Otherwise, please amend or remove this issue.	It is unclear what is meant by Key Issue 3 in general, and the EAG do not provide further explanation around this issue within the body of the report. The EAG point to Section 3.2 of the report, however, there is no further detail of this issue in this section. While there is some more detail on page 68, it involves a factual inaccuracy (please see above).	

Issue 2 Additional analyses suggested by the EAG

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Request to conduct a similarity assessment between the populations in the model and in the clinical trials as a way which may help to resolve Key Issue 7 – page 15	Page 15: Please provide more detail to explain what is meant by “Conducting a similarity assessment between the populations in the model and in the clinical trials.” As additional evidence or analyses which might help to resolve Key Issue 7.	It is unclear what the EAG suggest, and it would be helpful to see additional detail as to what this similarity assessment involves.	This remark was a copy/pasting error and has been removed for this Key issue
Request to conduct a similarity assessment between the populations in the model and in the clinical trials as a way which may help to resolve Key Issue 8 – page 16	Page 16: Please provide more detail to explain what is meant by “Conducting a similarity assessment between the populations in the model and in the clinical trials.” As additional evidence or analyses which might help to resolve Key Issue 8.	It is unclear what the EAG suggest, and it would be helpful to see additional detail as to what this similarity assessment involves.	We have changed to wording to that used for Key Issue 6 and added an example: Evidence supporting the alignment of the chronic population in the model and in REACH3 , such as a comparison of utilities of REACH2 patients who developed cGvHD and utilities of REACH3 patients who had SR-aGvHD.

Issue 3 Misleading and inaccurate description of company position

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
The wording used in relation to the company position regarding providing a subgroup analysis of ruxolitinib vs BAT by treatment, and including ECP subgroups – page 21 and page 68	Page 21 and page 68: Please change "refused" to "did not consider it appropriate".	We provided a justification to explain why we did not consider it appropriate to provide a subgroup analysis of ruxolitinib vs BAT by treatment, i.e., this analysis would break randomisation. Regarding ECP subgroups, clinicians have confirmed that they do not see patients with good venous access/who are haematologically stable as a separate subgroup, and instead there are a multitude of factors that decide whether a patient can receive ECP or not (please see "Validation calls to support CQs" report submitted as part of reference pack for Response to EAG CQs). Therefore, there are no subgroup data available for patients who received ECP, as they cannot be classified into separate subgroups	Not a factual inaccuracy.

Issue 4 Unclear EAG statements

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
The EAG state that there may potentially be a mismatch between the intervention dose and concomitant treatments between the REACH trials and UK clinical practice – page 22	It is unclear why the EAG believe there is a mismatch between the REACH trials and UK clinical practice, and whether this is their view, or the opinion of their clinical experts. Please amend this statement to make this clear. Please also amend this statement to include that the intervention dose has been validated by clinical experts as part of the CS (see more detail in "justification for amendment" column).	Within the Validation Reports as provided in the reference pack of the original CS (page 4), it is explained that the clinical expert noted the 10mg BID dosing as per REACH2 is appropriate for the population of interest and reflective of UK clinical practice.	Not a factual inaccuracy – the EAG state that there could be a mismatch, not that there is one.

Issue 5 Statistical information not provided when discussing overall survival (OS) for ECP

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
The EAG mention that "if life is also extended for ECP patients, which seems to be the case based on Figure 9 in the clarification letter response, the total costs of the ECP arm could increase as well", although it is not mentioned that this is not statistically significant – page 78	Please add the hazard ratio (HR: 1.118, p=0.639) as provided in Figure 9 of the clarification response.	It is important to include the HR as it provides the full context to the reader when considering the opinion of the EAG.	We have changed this text to: But if life is also extended for ECP patients, which might be the case based on Figure 9 in the clarification letter response (HR: 1.118, p=0.639),

Issue 6 Additional factual inaccuracies

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Discrepancy in figure in tables 1.10, page 17 and 6.8, page 134	Column “Total costs” and row “(1) + Ruxolitinib only different time to NST” change: 82,579 to **82,580**	The number needs to be rounded up	Corrected
Referring to the wrong trial, page 68	Please change “The clinical effectiveness systematic review revealed two trials of the intervention, the key one being REACH2, which is an RCT comparing ruxolitinib to BAT, the other being REACH2, which is a single arm trial.” to “The clinical effectiveness systematic review revealed two trials of the intervention, the key one being REACH2, which is an RCT comparing ruxolitinib to BAT, the other being **REACH1*,*** which is a single arm trial.	The wrong trial is being referred to in the second part of this sentence.	Corrected.
Phrasing of sentence, page 76	Please change: “However, the economic model uses data from REACH3 to model (survival and QoL) outcomes for patients developing cGvHD” to	In REACH2, some patients are developing cGvHD from aGvHD, but in REACH3, patients have already developed cGvHD	This sentence does not need changing, as our statement, that REACH 3 data is used for patients in the model developing cGvHD, is exactly in line with the

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
	"However, the economic model uses data from REACH3 to model (survival and QoL) outcomes for patients **who have developed** cGvHD"		explanation given by the company.
Inaccurate distribution listed, page 80	Please change: "Various standard survival distributions were assessed including the exponential, gamma, generalised gamma, Gompertz, log-logistic, log-normal, and Weibull distributions" to "Various standard survival distributions were assessed including the exponential, generalised gamma, Gompertz, log-logistic, log-normal, and Weibull distributions"	Gamma distribution was not fitted	Corrected
Phrasing of sentence, section c) ii, page 82	Please change: "it was not considered plausible to assume that the risk of failure or relapse would be higher" to "it was not considered plausible to assume that the risk of failure **due to death or** relapse would be higher"	Relapse is part of failure, and REACH2 does no show that the risk of failure is higher for ruxolitinib, the main thing it shows is that the risk of failure is lower.	Corrected
Phrasing of sentence, section e), page 82	Please change: "the company stated that independent models were selected irrespective of the crossing of the log-log curves"	Crossing log-log curves would be an argument in favour of individual models	Corrected

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
	to "the company stated that independent models were selected **despite crossing curves"**		
"Gamma" used when should be "Generalised gamma" pages 82–83	Please change: "clinical experts preferred the Gompertz and gamma models" to "clinical experts preferred the Gompertz and **generalised** gamma models"	To correct inaccuracy	Corrected
Cost per readmission, page 103, section b), page 116, section 5.3.2.1 page 121, paragraph 3, pages 138–139	Please change: Pages 103, 121 and 138–139 "the EAG finds a current cost of £14,624 " to "the EAG finds a current cost of £**13,342**" Page 116: "the EAG found a current cost of £14,624". to "the EAG found a current cost of £**13,342**"	PSSRU 2023 Table 12.1.1. NHSCII pay and prices are used for inflating £10,091 at 2010 price, results in £13,341.66 in 2023 value.	The EAG wants to thank the company for checking the EAG derived cost estimate and finding an error. We have made the requested changes and added a footnote on page 103: The EAG had estimated a cost of £14,624 initially. However, during the factual error check, the company pointed out that the EAG had also made an error in the indexing of the 2010 cost for

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG comment</th></tr>
<tr><td></td><td></td><td></td><td>readmission and they provided the correct corrected value.

As a consequence of this change, all results in the report have been updated.</td></tr>
<tr><td>Inaccuracies in Table 4.20, pages 103–104 in frequency columns</td><td>Please change the frequencies for Hypertension, Neutrophil count decreased, White blood cell count decreased and Acute Kidney injury for both ruxolitinib and BAT frequency columns so that they match those in Table 26 of the CS.

Please note that as the hypomagnesaemia row will need to be changed as listed under Issue 9, we have added the correct values listed above to the new Table 4.20</td><td>To correct inaccuracies in data points</td><td>Corrected</td></tr>
<tr><td>Inaccuracies in Table 6.6, page 131, row “Transition probabilities from the naïve analysis”</td><td>Please change:
<table><tr><td>Transition probabilities from the naïve analysis</td><td>[redacted]</td><td>[redacted]</td><td>28,988</td><td>24,156</td></tr></table>to
<table><tr><td>Transition probabilities from the naïve analysis</td><td>[redacted]</td><td>[redacted]</td><td>23,381</td><td>19,484</td></tr></table></td><td>To correct inaccurate results from analysis</td><td>Corrected</td></tr>
</table>

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Inaccuracies in Table 6.7, page 133	See amended table below with changes in **bold** (including in scenario description)	To correct inaccurate results from EAG's analysis in Scenario analyses set 1. For Scenario analyses set 2, in the EAG 'Other hospitalisation rate' scenario, incorrect inflated cost of initial hospitalisation was used (£14,624 instead of £13,341). On the 'Cost data' sheet in the electronic model, Cell C55 should be £13,341.66, and cell C65 and C66 should both be £1,520.75 (£13,341.66 * 0.114 per 4-week cycle) when running this scenario. By using incorrect cost values, the results of this scenario will be inaccurate	All results in the report have been changed to reflect the correct hospitalization costs.
Description of method for calculating drug acquisition costs, page 138	Please change: "Drug acquisition costs are based upon costs per mg, while NICE recommends the use of costs per pack" to	To correct inaccurate description	The text is not factually incorrect, but the EAG has changed the wording as suggested

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
	"Drug acquisition costs are based upon costs per mg, **which are based on cost per pack and pack size"**		

Table 6.7 in EAG report

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	ICER (£/QALY) with severity modifier
EAG base-case	[redacted]	[redacted]	21,815	18,179
Scenario analyses set 1: derivation and implementation of HRQoL in the model				
aGvHD FF long-term health state utility values higher than those of cGvHD patients	[redacted]	[redacted]	23,993	19,994
Equal utility value for acute and chronic GvHD NST health states	[redacted]	[redacted]	24,266	20,222
Separate statistical models for the utility values for aGvHD (REACH2) and cGvHD (REACH3) – Model 1	[redacted]	[redacted]	23,907	**19,922**
Separate statistical models for the utility values for aGvHD (REACH2) and cGvHD (REACH3) – Model 2	[redacted]	[redacted]	23,989	19,991
Separate statistical models for the utility values for aGvHD (REACH2) and cGvHD (REACH3) – Model 3	[redacted]	[redacted]	21,600	18,000
Separate statistical models for the utility values for aGvHD (REACH2) and cGvHD (REACH3) – Model 4	[redacted]	[redacted]	21,790	**18,159**
CADTH utility for responders after 12 weeks	[redacted]	[redacted]	23,603	**19,670**

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	ICER (£/QALY) with severity modifier
Scenario analyses set 2: resource use and costs				
ECP only for BAT	[redacted]	[redacted]	9,510	7,925
Reduce overall BAT costs with 25% - **1L**	[redacted]	[redacted]	27,595	22,996
Increase overall BAT costs with 25% - **1L**	[redacted]	[redacted]	16,034	13,362
Other hospitalisation rate	[redacted]	[redacted]	**24,188**	**20,157**
Costs MSC £20,000	[redacted]	[redacted]	20,075	16,729

Issue 7 Typographical errors

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG comment**
Wrong month for SLR searches –pages 70, 72 and 135	Please change: "Searches were conducted in November 2019" To "Searches were conducted in July 2019"	The clinical SLRs began in November 2019 but the non-clinical SLRs began in July 2019.	Corrected.
Typographical error in utility value, page 94	Please change: "the utility assumed for FF after four cycles is much higher (0.678)" to	As per CS and table 4.8 of the EAG report	Corrected

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
	"the utility assumed for FF after four cycles is much higher (**0.677)"**		
Wrong formulation size, pack size and reference for Everolimus in Table 4.17, page 99	Please change "2.5 mg" to "0.75 mg", "30 capsules" to "60 tablets" and the "eMIT" reference to "BNF" Please remove footnote "There are inconsistencies between the CS and the model with respect to the formulation size and pack size of everolimus. The numbers in the table present the information provided in the CS. In the model, the formulation size is 0.75 and the pack size is 60 capsules."	Formulation size was corrected to 0.75 mg and pack size to 60 tablets in the *Appendix of corrections and updated results* document submitted with the response to EAG CQs; the reference is as per original CS	Corrected
Typographical error in footnote page 120	Please change: "K139, K162, BS95, BS117, BS139 and BS162" to "K139, K16**1**, BS95, BS117, BS139 and BS16**1"**	To correct typographical error	Corrected

Issue 8 Incorrect marking

Location of incorrect marking in EAG report	Description of incorrect marking	Amended marking	EAG comment
Abbreviations, page 3	CiC marking missing for definition of [redacted]	[redacted]	Amended
Section 3.2.3, page 40	CiC marking missing for non-published REACH2 data "…whilst only [redacted]% received steroids as prior therapy in the BAT arm"	"whilst only [redacted] received steroids as prior therapy in the BAT arm"	Amended
Sections 3.2.5.1.2 and 3.2.5.1.3, page 61	All CiC marking is missing from sections 3.2.5.1.2 and 3.2.5.1.3 (non-published safety data from REACH2)	**Section 3.2.5.1.2:** During the randomised treatment period, in the ruxolitinib arm, the most frequent AEs by PT (all grades) suspected to be related to study treatment (in ≥5% of patients) were those of cytopenia, including thrombocytopenia ([redacted]%), anaemia ([redacted]%), platelet count decreased ([redacted]%), neutropenia ([redacted]%), WBC count decreased [redacted]%), neutrophil count decreased ([redacted]%), leukopenia ([redacted]%), as well as CMV infection (combined for PTs CMV infection reactivation: [redacted]% and CMV infection: [redacted]%). Similarly, most frequent Grade ≥3 AEs suspected to be related to ruxolitinib were those of cytopenia,	Amended

Location of incorrect marking in EAG report	Description of incorrect marking	Amended marking	EAG comment
		including thrombocytopenia ([redacted]%), anaemia ([redacted]%), platelet count decreased ([redacted]%), neutropenia ([redacted]%), WBC count decreased ([redacted]%), neutrophil count decreased ([redacted]%) and leukopenia ([redacted]%). In the BAT arm, the most frequent AEs by PT (all grades) suspected to be related to study treatment (in ≥5% of patients) were CMV infection (combined for PTs CMV infection reactivation: [redacted]% and CMV infection: [redacted]%), followed by those of cytopenia, including WBC count decreased [redacted]%), anaemia ([redacted]%) and platelet count decreased [redacted]%). Grade ≥3 AEs suspected to be related to study treatment in the BAT arm were primarily cytopenia PTs, including WBC decreased ([redacted]%) and platelet count decreased [redacted]%). **Section 3.2.5.1.3:** Up to Day 28, a similar proportion of patients in the ruxolitinib arm ([redacted]%) and in the BAT arm ([redacted]%) experienced an SAE. The incidence of Grade ≥3 SAEs was [redacted]% in the ruxolitinib arm and [redacted]% in the BAT arm. In the ruxolitinib arm, sepsis ([redacted]%) was the only Grade ≥3 SAE by PT observed in	

Location of incorrect marking in EAG report	Description of incorrect marking	Amended marking	EAG comment
		>5% of patients. In the BAT arm, CMV infection reactivation ([redacted]%), septic shock ([redacted]%) and respiratory failure ([redacted]%) were the most frequent Grade ≥3 SAE by PT. During the randomised treatment period, SAEs were observed in [redacted]% of patients in the ruxolitinib arm and [redacted]% in the BAT arm. The proportion of patients with Grade ≥3 SAEs was higher in the ruxolitinib arm ([redacted]%) than the BAT arm ([redacted]%). In the ruxolitinib arm, sepsis ([redacted]%), septic shock [redacted]%) and diarrhoea ([redacted]%) were the only Grade ≥3 SAEs by PT observed in ≥5% of patients. In the BAT arm, sepsis [redacted]%), septic shock ([redacted]%), pneumonia ([redacted]%) and CMV infection (combined for PTs CMV infection reactivation: [redacted]% and CMV infection: [redacted]%) were the only Grade ≥3 SAEs by PT occurring in ≥5% of patients.	
Section 3.2.5.2.1, page 64	CiC marking is missing for the incidence of ALT increased (non-published safety data from REACH2)	"…alanine aminotransferase (ALT) increased ([redacted]%), and lymphocyte count…"	Amended

Location of incorrect marking in EAG report	Description of incorrect marking	Amended marking	EAG comment
Section 3.2.6.2, page 67	CiC marking is missing for the 3rd and 4th bullet points (non-published efficacy data from REACH3)	• After crossover treatment period, ORR at Cycle 7 Day 1 for ruxolitinib was [redacted] (95% CI: [redacted]) and similar in line with the ORR observed at Cycle 7 Day 1 during primary analysis and interim analysis • Final analysis of FFS based on data collected from 329 subjects showed the 3-month and 6-month FFS probability was [redacted]% (95% CI: [redacted]) and [redacted]% (95% CI: [redacted]) for ruxolitinib and [redacted]% (95% CI: [redacted]) and [redacted]% (95% CI: [redacted]) for BAT, respectively	Amended
Section 3.6, page 68	CiC marking missing from descriptive sentence (non-published efficacy data from REACH2)	However, the cumulative incidence of cGvHD was [redacted] for ruxolitinib at all time points	Amended
Figure 5.3, page 110	Figure should not be marked CiC	As per Figure 3 in Appendix of corrections	Amended

Issue 9 Errors in original CS

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG comment</th></tr>
<tr><td>The EAG report shows at the top of page 102 the correct figure of “£1,006.18 per cycle for readmissions” However In Table 40 of the CS, this was erroneously shown as £1,006.16, and this has been replicated in Table 4.19</td><td>Please change
<table><tr><td>Failure-free (subsequent cycles)</td><td>1,006.16</td></tr></table>to
<table><tr><td>Failure-free (subsequent cycles)</td><td>1,006.18</td></tr></table></td><td>To correct typographical error</td><td>Corrected</td></tr>
<tr><td>Table 4.20 of the EAG report, page 103 is based on table 41 of the CS for the Cost per event and Reference columns. However, Novartis have identified the following errors that will need amending</td><td>Please see in bold changes to be made in Table 4.20 below. Please note changes in frequency columns also required for the new hypoalbuminaemia category, changed from hypomagnesaemia.
Please note as per comment above in Issue 6, page 8, we have added the frequencies that need to be corrected for Hypertension, Neutrophil count decreased, White blood cell count decreased and Acute Kidney injury</td><td>To correct errors</td><td>Corrected</td></tr>
<tr><td>There was an error in the “Time horizon = 20 years” scenario in the model (Cell AQ6 on the 'Control' sheet in the electronic model should be empty instead of</td><td>In Table 5.6, please change:
<table><tr><th colspan="6">Decision problem</th></tr><tr><td>Lifetime</td><td>Time horizon = 20 years</td><td>[redacted]</td><td>[redacted]</td><td>40,087</td><td>33,406</td></tr></table></td><td>To correct results in scenario analysis tables</td><td>Corrected</td></tr>
</table>

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG comment</th></tr>
<tr><td>showing '21'), which affects the values in Table 5.6 (page 112) and Table 6.6 (page 131) of the EAG report (This will also affect Table 11 of the Appendix of Corrections and updated results)</td><td>to
<table><tr><th colspan="6">Decision problem</th></tr><tr><td>Lifetime</td><td>Time horizon = 20 years</td><td>[redacted]</td><td>[redacted]</td><td>29,969</td><td>24,974</td></tr></table>In Table 6.6, please change:
<table><tr><th colspan="5">Decision problem</th></tr><tr><td>Time horizon = 20 years</td><td>[redacted]</td><td>[redacted]</td><td>28,375</td><td>23,646</td></tr></table>to
<table><tr><th colspan="5">Decision problem</th></tr><tr><td>Time horizon = 20 years</td><td>[redacted]</td><td>[redacted]</td><td>21,136</td><td>17,614</td></tr></table></td><td></td><td></td></tr>
</table>

Table 4.20 (EAG report)

Adverse event	Cost per event (£)	Source	Frequency ruxolitinib	Frequency BAT
Anaemia	410.69	TA949[36]		
Thrombocytopenia	427.06			
Hypertension	**543.55**		**6.58%**	**5.33%**
Pneumonia	576.05			
Sepsis	311.58			
Hyperglycaemia	428.03			

Adverse event	Cost per event (£)	Source	Frequency ruxolitinib	Frequency BAT
Cytomegalovirus infection reactivation	1,955.82	TA689[40]		
Neutropenia	377.81			
Diarrhoea	163.36			
~~Neutrophil count decreased~~	~~372.13~~			
Alanine aminotransferase increased	567.09			
Urinary tract infection	1,955.82			
Hypokalaemia	372.13	TA642[41]		
Neutrophil count decreased	**880.67**			
Platelet count decreased	2,055.69			
Hypo**albuminaemia**	543.55		**5.92%**	**8.00%**
White blood cell count decreased	**574.37**		**13.16%**	**8.67%**
Hypophosphatemia	372.13			
Oedema peripheral	576.05	Assumed same as pneumonia		
Pyrexia	576.05			
Acute kidney injury	**576.05**		**3.95%**	**4.67%**
Nausea	163.36	Assumed same as diarrhoea		
Vomiting	163.36			
Hypocalcaemia	372.13	Assumed same as hypophosphatemia		
Blood bilirubin increased	0.00	Abnormal lab tests excluded		
Total costs				

NICE 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]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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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 also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **Tuesday 8 October 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, 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 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.

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Part 1: Treating graft versus host disease and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Fiona Dignan
2. Name of organisation	Manchester University NHS Foundation Trust and NHS England
3. Job title or position	Consultant Haematologist National Specialty Advisor for Blood and Marrow Transplantation CRG
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with graft versus host disease ? ☒ A specialist in the clinical evidence base for graft versus host disease or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for graft versus host disease?	Acute graft versus host disease (GVHD) occurs following a stem cell transplant. The condition affects the skin, gastro-intestinal tract and liver. Patients notice

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	skin rashes which can vary between mild eczematous type rashes to severe blistering of the skin. Involvement of the gut can lead to sickness and diarrhoea. The diarrhoea can be very severe. Liver involvement can lead to jaundice and liver failure if not treated. The aim of therapy is to treat the symptoms of GVHD so that they have less impact on the day-to-day life of the patient. In addition, severe GVHD can lead to prolonged hospital admissions and death and treatment is used to try and avoid these complications.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Acute graft versus host disease is graded depending on the clinical symptoms and signs of the disease. A clinically significant response would be a complete resolution of symptoms and signs of the disease or partial resolution of symptoms and signs of the disease. A reduction in the use of other immunosuppressive drugs including steroids is also clinically significant as this reduces the risks associated with steroid use.
10. In your view, is there an unmet need for patients and healthcare professionals in graft versus host disease?	Yes, there is an unmet need for patients with graft versus host disease that does not respond to steroids. There is a lack of effective treatment options for this group of patients leading to significant morbidity from GVHD symptoms, infections due to immunosuppression and mortality.
11. How is graft versus host disease currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	The pathway is clearly articulated in the NHSE commissioning policy and the joint BCSH and BSBMTCT guidelines. The commissioning policy includes extracorporeal photopheresis (ECP) as the only treatment for patients who fail first line treatment. The inclusion criteria are included below: Inclusion criteria: (i) Patient presents with continued or relapsed clinical features of aGvHD (maculopapular rash; persistent nausea and/or emesis; abdominal

	cramps with diarrhoea; and a rising serum bilirubin concentration) as determined by clinical examination OR biopsy where disease constellation is not clear; AND (ii) Is unsuitable for, is steroid-dependent OR shows incomplete response to first-line treatment (combination therapy of topical therapies, calcineurin inhibitors, systemic corticosteroids, sirolimus and/or mycophenolate mofetil). In the Joint BCSH and BSBMTCT guidelines other second line treatments are suggested including IL 2 receptor antibodies, anti-TNF antibodies, MTOR inhibitors and mycophenolate mofetil in addition to ECP. Third line options listed include methotrexate, pentostatin, mesenchymal stem cells or alemtuzumab. Despite this guidance there is some variation in practice. Some professionals are able to access mesenchymal stem cells or etanercept and may use these agents instead of or in addition to ECP. If ruxolitinib was available it would be used instead of ECP in patients who fail first line therapy with steroids. Other treatments including ECP would be reserved for patients who did not response to ruxolitinib.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)	The current treatment for patients who have failed first line therapy with steroids is extracorporeal photopheresis. This treatment involves an apheresis procedure and has to take place in a hospital setting either as an in-patient if a patient is admitted for other reasons or in the out- patient setting. The usual schedule is two treatments per week for 8 weeks when it is used for acute graft versus host disease. Patients often need to attend the hospital for several hours and may require a blood transfusion before treatment. An indwelling central venous catheter called a tesio line is often required for venous access. Blood tests are required prior to therapy.

• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The new technology (ruxolitinib) is an oral drug. It would be prescribed in a specialist clinic by physicians who are experienced in the management of graft versus host disease. There would be no need for new facilities or equipment and many physicians are already familiar with using ruxolitinib as it was used during the covid pandemic as part of a rapid commissioning policy. Many physicians are also used to using ruxolitinib in the management of patients with myelofibrosis or myeloproliferative disorders so are experienced in the management of side effects.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	The Reach 2 trial (Zeiser et al, 2020, New England Journal of Medicine) was a multicentre, randomised, open-label, phase 3 trial comparing he efficacy and safety of oral ruxolitinib with the investigator's choice of therapy from a list of 9 commonly used options. The mean failure free survival was considerably longer with ruxolitinib compared to the control arm (5 months compared to 1 month, hazard ratio 0.46 95% CI, 0.35-0.60). The median overall survival was 11.1 months in the ruxolitinib arm compared to 6.5 months in the control arm. Hazard ratio for death 0.83, 95% CI 0.6-1.15. I would expect the technology to increase health related quality of life more than current care as it is much easier to deliver. Patients would need to spend less time at the hospital as ruxolitinib is an oral treatment that can be given at home. This mode of delivery is likely to be preferable to having to spend several hours at the hospital receiving ECP therapy. It is also likely to make a particular difference for patients who have to travel a long way to the specialist centre to receive therapy.

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	It would be easier to use than the current treatment options as it is an oral drug (see Q12). There are no significant practical implications for its use. Patients would need to have blood tests taken prior to treatment and during treatment but this is standard of care for this group of patients
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Ruxolitinib therapy would not require any additional testing. Patients would be monitored for infections and also have their full blood counts, liver and renal function monitored but this would be standard of care following a transplant. Ruxolitinib would be stopped if patients developed side effects as a consequence of the drug including significant cytopenias or infectious complications. It would also be stopped if there was no complete or partial response observed in the patient's acute GVHD symptoms.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen	The treatment is more easily administered as it is an oral therapy than the current standard of care treatment. It is therefore likely to involve less hospital visits which is likely to improve patients' quality of life. Some patients who have had a stem cell transplant live a long distance away from the transplant centre and reducing the number of visits to the hospital and the length of time spent at these visits can significantly improve their quality of life.

may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes, I would consider ruxolitinib to be a step-change in the management of acute graft versus host disease. It is an oral therapy with minimal side effects that has been shown in a randomised controlled trial to be effective in the management of acute GVHD. There is an unmet need for effective treatment in patients who fail first line therapy of acute graft versus host disease. The use of ruxolitinib would address this unmet need.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The main side effects of ruxolitinib are low blood counts and the risk of infections. If these occur then patients may need to receive a dose alteration of ruxolitinib. It might sometimes be necessary to give a blood transfusion or intravenous antibiotics. These problems are very common following a stem cell transplant anyway and it is unlikely that ruxolitinib would significantly decrease a patient's quality of life.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The Reach-2 randomised controlled trial does reflect current UK practice. Oral ruxolitinib was compared to best available therapy. This included 9 different therapies including etanercept, mycophenolate and sirolimus. The majority of patients received extra-corporeal photopheresis as best available therapy which would reflect UK practice. The most important outcomes were overall response at day 28 and day 56 which were measured in the trial. There were no adverse events that were not apparent in clinical trials that have subsequently come to light
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Please see below regarding UK audit data

22. How do data on real-world experience compare with the trial data?	Ruxolitinib was available for patients with acute graft versus host disease during the covid pandemic as part of a rapid commissioning policy Trial data were reflected in a UK audit that was undertaken of the use of ruxolitinib during the covid pandemic. Forty-eight patients received ruxolitinib for acute GVHD. 37 patients had a complete or partial response to therapy at day 28 and 24 had a complete or partial response by day 56 (Nick Duncan, personal communication, BMT CRG ruxolitinib data)
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population	This technology will reduce health inequalities because it will offer an alternative treatment option to ECP. This would benefit individuals who have difficulties and challenges with travelling to receive ECP either due to work or caring commitments, disability or other reasons. As described above, patients must travel to a specialist centre to receive ECP on a regular basis. Some patients live a long distance away from the centre and rely on patient transport services which mean that they can be reluctant to receive the treatment as it can often mean spending two full days away from home. The new technology (ruxolitinib) is an oral tablet which patients can take at home. Inequality currently exists in the management of patients with acute graft versus host disease as some NHS provider trusts have agreed local funding for ruxolitinib whereas some centres are not able to fund the treatment.

• lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Ruxolitinib is an oral drug with manageable side effects

There is good quality evidence supporting the use of ruxolitinib in the management of acute graft versus host disease

Ruxolitinib addresses an unmet need for this patient population

Ruxolitinib has less resource implications than the current standard of care

Staff are already familiar with using ruxolitinib so minimal training would be required

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with graft versus host disease or caring for a patient with graft versus host disease. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

NICE National Institute for Health and Care Excellence

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

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Your response should not be longer than 15 pages.

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Patient expert statement

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

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with graft versus host disease

Table 1 About you, graft versus host disease, current treatments and equality

1. Your name	Elsa Bennett
2. Are you (please tick all that apply)	☐ A patient with graft versus host disease? ☐ A patient with experience of the treatment being evaluated? ☒ A carer of a patient with graft versus host disease? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Anthony Nolan
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert

	engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with graft versus host disease? **If you are a carer (for someone with graft versus host disease) please share your experience of caring for them**	My husband, Steve, had his first stem cell transplant on 28/11/19 with a top up stem cell transplant on 21/8/20 and had GvHD from December 2019 – February 2022. He had GvHD of his skin, eyes, mouth and gut. His GvHD was so severe that the complications arising from it and the associated treatments resulted in 9 episodes of sepsis requiring hospital admission and extended stays from February 2020 – December 2021. When Steve was at home he required 24hrs nursing care from me as he was so weak and had extreme fatigue, he could barely get out of bed and struggled to walk as far as the bathroom at times. This impacted severely on the time I was able to give our children (they were 17 at the time of Steve's transplant) as Steve needed such intense support, and they in turn helped out with his care when they could. It was extremely stressful for them to see their Dad so acutely unwell especially when at times he became confused with altered behaviour. At his most ill he required 38 different medications given throughout the day and night which I was responsible for. I was constantly on alert monitoring all his symptoms and providing all his care as we just wanted to keep him out of hospital so that he could be at home with us where he wanted to be. I felt unable to switch off in case I missed any life-threatening changes and was constantly weighing up what action to take and liaising with all the health professional involved in his treatment. This was physically and mentally exhausting and very stressful when I had to make the decision that he required treatment and care in hospital as Steve was sometimes opposed to this and I then had to make the decision to override him and act in his best interest. Steve's skin was severely affected and caused him much pain and discomfort. I had to apply creams every hour over his whole body to try and alleviate the discomfort. It would take me almost an hour to gently apply them and then I would need to start

	all over again as his skin was so dry, inflamed and cracked and put him at huge risk of infection. It also meant the bed linen needed changing and washing almost every day as the creams and lotions applied were so messy. He was unable to bathe himself so I also had to do this for him which was really difficult as I had to use aids to get him in and out of the bath as he was unable to do this himself. His skin caused him such pain that it was difficult for him to move and this was very hard to witness. The analgesia required made him very drowsy at times which made the applying of creams and lotions even more tricky and very trying for Steve. GvHD affected Steve's eyes to a lesser extent. His eyes felt very dry and gritty all the time and became infected from time to time. He required eye drops ranging from 2 – 4 times a day which I administered as he was too unwell to do this himself. The oral GvHD was very severe. Steve's tongue was covered in lesions causing acute pain all the time and made it almost impossible for him to talk. Eating and drinking was very challenging. I had to help him have steroid mouth washes every 4 hours interspersed with oral analgesia sprays. He then required appointments at The Eastman Dental Hospital to treat his oral lesions which was an additional challenge getting there and back when Steve felt so ill and required huge planning on my part to take all the required medications and supplies with us for a 6 hour round trip. He couldn't eat so lost a huge amount of weight which increased his weakness, muscle loss and fatigue and risk of infection as he was so nutritionally compromised. We then followed a high calorie diet advised by the Oncology Dietitian, and I was constantly trying to get Steve to eat even the tiniest amounts and preparing special foods for him to try. It was awful seeing him just waste away and struggling to eat and drink. Meals have always been an integral part of our family life so this was an enjoyable everyday part of our lives that was severely impacted for all of us. The gut GvHD was also very severe. This caused Steve a great deal of acute pain, frequent and profuse diarrhoea, Melena and Oesophagitis. The diarrhoea was so extreme that it resulted in incontinence which was very embarrassing and deeply

	unpleasant for Steve. In these instances I would be clearing this up and providing intimate care for him. This obviously resulted in more laundry for me to do and cleaning of carpets and flooring. The diarrhoea had a severe impact on his overall wellbeing understandably and again was very hard to witness. It also resulted in him having perianal ulcers and a fistula which were excruciatingly painful and required redressing every time he opened his bowels. This was a very intimate procedure which I carried out numerous times a day, and although I did this willingly it did make me feel that I just wanted to be Steve's wife and not his carer and nurse. Steve required a very high level of nursing care at home when he was not in hospital during the 2 years he had GvHD, and there were additional complex care needs caused by the treatment of GvHD with steroids which I will discuss in section 8. He was frequently only discharged from hospital precisely because I am a nurse and was able to provide the care he needed and understand the implications and signs of when he was deteriorating again. At the time, in the full whirlwind of coping with extreme illness and holding our family together, I didn't much consider the impact this was having on me but now I recognise that this affected me at a very deep level. We were very fortunate that I had very sympathetic employers at the time who gave me unlimited paid time off to care for Steve. I did ultimately decide to stop working and resigned from my post so that I could be Steve's full-time carer at a point when our future was very uncertain. I should also add that as Steve's carer I had a very strong supportive network of friends, family and colleagues. Steve was prescribed Ruxolitinib from July 2020 – February 2022 it had an almost immediate impact on all his GvHD symptoms and did eventually resolve his GvHD. It was life changing and life saving for him.

7a. What do you think of the current treatments and care available for graft versus host disease on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	I think the initial treatment such as oral steroid medication in the early stages of GvHD is acceptable. However, when ever increasing doses of oral and IV steroids are required which cause unpleasant side effects and do not resolve GvHD then I think more options need to be available. Extracorporeal photopheresis is a very lengthy treatment which was offered to Steve when he was already severely compromised/unwell and was yet another invasive procedure to endure. He was in fact too ill to undergo ECP so again this might not be appropriate or effective treatment for someone with severe GvHD. The care given by the NHS staff for Steve's GvHD was outstanding. I am aware through patient and families' forums that my views on these current treatments compare similarly. There is a strong feeling that where there is a clinical indication for a person to receive Ruxolitinib to treat their GvHD then this should be an available option on the NHS.
8. If there are disadvantages for patients of current NHS treatments for graft versus host disease (for example, how they are given or taken, side effects of treatment, and any others) please describe these	The disadvantages of current NHS treatments for GvHD in our experience are as follows : ECP – This can only be carried out at specialist centres. This means for a person who is already severely compromised and fatigued that they usually have to travel for several hours when they are feeling unwell which is very unpleasant. Travelling when you are immunocompromised and have GvHD puts you at risk of exposure to infection leading to severe illness and hospitalisation. There are also financial implications for the patient if they have to travel a considerable distance and also need someone to accompany them. Steroid treatment – the side effects of high doses of steroids caused Steve significant and debilitating complications requiring input from many specialists within the NHS, so the side effects have huge cost implications for all the further hospitalisation and treatments required.

	He developed steroid induced hyperglycaemia resulting in having to use insulin for 18 months. Initially he was too unwell to be able to self-administer this, so I had to monitor his blood glucose levels and give him insulin with subcutaneous injections. He had frequent hyper episodes resulting in being ketotic and needing intravenous fluids and additional insulin to resolve this. These episodes were frightening for us all as Steve became very confused and unwell and needed a swift response to correct this. It was difficult to manage this for Steve as he needed a high calorie diet as he was malnourished but at the same time his blood glucose levels were very erratic and so we had to carefully monitor everything he ate and then adjust the insulin he required accordingly. The steroid treatment caused Steve to develop Posterior Subcapsular Cataracts. This meant that he could not see clearly, he struggled to read and watch television. Steve is an avid reader and, for someone in his position who was too unwell and fatigued to be very active, reading and keeping in touch with friends via email and text messages was essential for his mental health and wellbeing. So, it was extremely frustrating and depressing for him to have impaired vision. He required cataract surgery on both eyes and then follow up laser treatment. A long-term side effect Steve has is reduced bone density/osteoporosis. This requires him to take medication twice a day and to have bone density scans to monitor it. Whilst receiving high doses of intravenous steroids during hospital admissions to treat his GvHD they also caused him to have insomnia and hallucinations which was deeply unpleasant and frightening for Steve. All these side effects had a very severe effect on Steve's quality of life, diminishing it significantly at a time when he needed all his mental strength and resources to deal with his recovery from Acute Myeloid Leukaemia and 2 stem cell transplants.
9a. If there are advantages of ruxolitinib over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability	Steve was treated with Ruxolitinib from July 2020 until February 2022 and the advantages over current treatments were: He was able to take the medication orally at home rather than being in hospital.

to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does ruxolitinib help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	His quality of life was transformed as it resolved his GvHD, without it his survival was questionable. It enabled Steve to take control of his own care in many ways from self-care to being able to make decisions and be able to think clearly again. He was able to participate fully in family life. He did not experience any side effects unlike with all the other previous treatments. The most important advantage was that it resolved Steve's GvHD which had seemed intractable and therefore his quality of life was transformed. Ruxolitinib negates the need to have to travel to receive treatment at a time when you are already very unwell. It does not cause all the side effects, some of which can be life threatening, which result in the need for further complex treatment from specialists within the NHS thereby reducing the amount of time spent in hospital. It reduces the recovery time of the individual and thereby improves their health and wellbeing.
10. If there are disadvantages of ruxolitinib over current treatments on the NHS please describe these. For example, are there any risks with ruxolitinib? If you are concerned about any potential side effects you have heard about, please describe them and explain why	We did not experience any disadvantages.
11. Are there any groups of patients who might benefit more from ruxolitinib or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility,	I think all patients with GvHD would benefit equally from having access to Ruxolitinib.

dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering graft versus host disease and ruxolitinib? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	I think for people with lower incomes the financial burden of travelling to treatment centres for ECP puts them at a particular disadvantage which they wouldn't experience if they could be treated with Ruxolitinib at home. Older people and those with disabilities might also find it much more challenging to travel to ECP treatment centres and thereby experience a greater disadvantage than others.
13. Are there any other issues that you would like the committee to consider?	No.

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Acute GvHD is a life-threatening complication following stem cell transplant and has a huge and traumatic impact on the patient and their family.
- The treatments currently available to treat acute GvHD on the NHS are not always effective and cause many unpleasant and debilitating side effects impairing the quality of life for the patient.
- Ruxolitinib is an effective and lifesaving treatment. It is a much kinder treatment than many of the current treatment options available.
- All patients with acute GvHD who would benefit from treatment with Ruxolitinib should have equal access to this on the NHS

Thank you for your time.

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Single Technology Appraisal

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

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with graft versus host disease or caring for a patient with graft versus host disease. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

NICE National Institute for Health and Care Excellence

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Tuesday 8 October 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, 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 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.

Patient expert statement

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

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with graft versus host disease

Table 1 About you, graft versus host disease, current treatments and equality

1. Your name	Mr Kenneth David Dawson
2. Are you (please tick all that apply)	☒ A patient with graft versus host disease? ☒ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with graft versus host disease? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Anthony Nolan
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert

	engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with graft versus host disease? **If you are a carer (for someone with graft versus host disease) please share your experience of caring for them**	In April 2022 I was diagnosed with Myelodysplasia Syndrome and in August 2022 I was given a stem cell transplant. I first developed Graft Versus Host in November of that year and was given Topical Steroids which initially was Betnovate, however the rash worsened later in the month and oral steroids prescribed, (Prednisolone). The rash appeared to settle, and steroids were reduced but flared up again in January 2023. The steroids were restarted and supplemented in February with ECP treatments, initially 2 days a week on alternate weeks. Also, my veins collapsed through the regularity of inserting cannulas, therefore I had to have a Hickman line fitted. At this point I found the ECP treatment to be time consuming taking at least 2 hours for every attendance. These coupled with weekly clinic appointments and regular blood transfusions meant that hospital visits had a detrimental effect on my work and social life. In May 2023 the ECP was increased to 3 times a week as my skin was not improving, in fact the rash was now so bad that I had to apply Dermovate, Hydrocortisone Creams and Hydromol twice a day over my entire body. In addition, my skin was severely shedding and was unsightly, also my skin could not regulate temperature in the normal way, and I was constantly shivering and feeling cold. Also my skin was incredibly itchy and my sleep was interrupted. Things became so bad that I had to be hospitalised. Unfortunately, at this stage I was not tolerating the steroids which were now causing a negative psychological effect. In view of the severity the steroids were gradually reduced. In June 2023 after discussion with my Consultants I started taking Ruxolitnib, (5mg), I tablet twice a day, which I self-funded. Within only 1 month there was a huge

	improvement in my skin. ECP was stopped shortly after this. Ruxolitnib was so effective that the dose was reduced in October to 1 tablet daily and finally stopped in November. My experience was I tolerated Ruxolitinib very well with no recognisable side effects. This had a dramatic improvement on my quality of life, no ECP appointments, no creams to apply and no steroids.
7a. What do you think of the current treatments and care available for graft versus host disease on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	Although I am extremely grateful for the Graft Versus Host treatments I was given, in my case they seemed ineffective. Also, they were time consuming and seemed to be not cost effective to the NHS from a lay person's point of view.
8. If there are disadvantages for patients of current NHS treatments for graft versus host disease (for example, how they are given or taken, side effects of treatment, and any others) please describe these	ECP treatment- Extremely time consuming and labour intensive. Steroids- Liable to damaging physical and psychological side effects.
9a. If there are advantages of ruxolitinib over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does ruxolitinib help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	9a) In my case Ruxolitinib greatly improved my quality of life in a very short time. The ability to take tablets at home, reducing the number of hours spent in hospital appointments every week. 9b) Both of the above equally. 9c) Ruxolitinib helped to address the disadvantages of current treatments by how quickly it improved the Graft Versus Host, without the need for Steroid intervention.

10. If there are disadvantages of ruxolitinib over current treatments on the NHS please describe these. For example, are there any risks with ruxolitinib? If you are concerned about any potential side effects you have heard about, please describe them and explain why	None that I am aware of.
11. Are there any groups of patients who might benefit more from ruxolitinib or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	None from my experience and knowledge.
12. Are there any potential equality issues that should be taken into account when considering graft versus host disease and ruxolitinib? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	Not in my knowledge.

13. Are there any other issues that you would like the committee to consider?	There are none from my side.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Convenience for both patient and clinicians, to be able to use at home.
- Avoidance of lengthy hospital appointments and admissions.
- Speed of effectiveness.
- Quality of life for patient greatly improved.
- Lack of side effects compared to other treatments.

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