SMC2750

ruxolitinib tablets (Jakavi®)

Novartis

09 May 2025

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the end of life and orphan equivalent medicine process

ruxolitinib (Jakavi®) is accepted for use within NHSScotland.

Indication under review: for the treatment of patients aged 12 years and older with acute graft versus host disease who have inadequate response to corticosteroids.

In a randomised, open-label, phase III study, ruxolitinib treatment resulted in a statistically significant improvement in overall response rate compared with best available therapy in patients aged 12 years and older with acute graft versus host disease who have inadequate response to corticosteroids.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or PAS/ list prices that are equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Ruxolitinib is a Janus Associated Kinase (JAK) inhibitor with selectivity for JAK1 and JAK2. Ruxolitinib interferes with JAK1 and JAK2 signalling pathways thereby preventing the development, proliferation and activation of immune cells in graft versus host disease.[1]

For this indication, the recommended starting dose of ruxolitinib is 10 mg orally twice daily; the dose may be titrated based on efficacy and safety. Tapering of ruxolitinib may be considered in patients with a response and after having discontinued corticosteroids. See the summary of product characteristics (SPC) for further information.[1]

1.2. Disease background

Graft versus host disease (GvHD) is a major complication following allogenic haematopoietic stem cell transplantation (alloSCT). AlloSCT is a treatment for patients with malignant and non-malignant haematological conditions, and for specific immunological diseases. In patients with GvHD, immune cells from the donor recognise the recipient's tissues as foreign and mount an immune response against the recipient's cells. GvHD can be defined as acute (aGvHD) or chronic (cGvHD). The distinction between aGvHD and cGvHD is based on clinical presentation, specific diagnostic criteria and tissue pathology. Acute GvHD predominately affects the skin, gastrointestinal tract and liver.[2, 3]

In 2022, there were 1,547 alloSCT cases in the UK. Approximately 34% to 53% of patients develop aGvHD following alloSCT and 50% of patients with aGvHD develop steroid-refractory aGvHD.[4, 5]

Quality of life is poor for patients with steroid-refractory aGvHD; these patients typically experience a high and severe symptom burden compared with patients who are steroid responsive.[6] Patients with steroid-refractory aGvHD have a poor prognosis, the median overall survival (OS) with current best available therapy is less than 6 months.[7, 8]

1.3. Treatment pathway and relevant comparators

Systemic treatment with corticosteroids is recommended first-line for patients with grade II (moderate) to IV (very severe) aGvHD, alongside ciclosporin with or without mycophenolate mofetil.[9] There is no standard of care for patients with steroid-refractory aGvHD and choice of treatment would be dependent on predominant site of GvHD. Treatments used include extracorporeal photopheresis (ECP), mesenchymal stem cells (MSCs), faecal microbiota transplant (FMT), alpha-1 antitrypsin, anti-thymocyte globulin (ATG) and off-label immunosuppressant medicines such as calcineurin inhibitors (ciclosporin, and tacrolimus), mTOR inhibitors (sirolimus) interleukin inhibitors (tocilizumab and ustekinumab), anti-lymphocyte monoclonal antibodies (alemtuzumab and vedolizumab), mycophenolate mofetil and tumour necrosis factor alpha (TNFa) inhibitors (etanercept and infliximab).[10] Clinical experts note that ruxolitinib may also be used via an Individual Patient Treatment Request.

1.4. Category for decision-making process

Ruxolitinib received an Innovation Passport allowing entry into the Innovative Licensing and Access Pathway.

Ruxolitinib meets SMC end of life and orphan equivalent criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of ruxolitinib for the treatment of aGvHD with an inadequate response to corticosteroids comes from REACH2.[11] Details are summarised in Table 2.1

Table 2.1. Overview of relevant study

Criteria	REACH2[11]
Study design	International, randomised, open-label, phase III study
Eligible patients	• Patients ≥12 years of age with grade II (moderate) to IV (severe) aGvHD as per MAGIC criteria, having previously undergone allogenic stem cell transplantation from any donor source with evident myeloid and platelet engraftment. • Confirmed diagnosis of steroid-refractory aGvHD, defined as patients administered high-dose systemic corticosteroids (methylprednisolone 2 mg/kg/day [or equivalent prednisone dose 2.5 mg/kg/day]), given alone or combined with calcineurin inhibitors (ciclosporin or tacrolimus) and either: ○ A) Progression based on organ assessment after at least 3 days compared to organ stage at the time of initiation of high-dose systemic corticosteroid with or without calcineurin inhibitor or, ○ B) Failure to achieve at a minimum partial response based on organ assessment after 7 days compared to organ stage at the time of initiation of high-dose systemic corticosteroid with or without calcineurin inhibitor or, ○ C) Patients who fail corticosteroid taper, defined as either: • Requirement for an increase in the corticosteroid dose to methylprednisolone ≥2 mg/kg/day (or equivalent prednisone dose ≥ 2.5 mg/kg/day) or, • Failure to taper the methylprednisolone dose to < 0.5 mg/kg/day (or equivalent prednisone dose < 0.6 mg/kg/day) for a minimum of 7 days.
Treatments & randomisation	Patients were randomised equally to oral ruxolitinib 10 mg twice daily (n=154) or investigator's choice of BAT (n=155). BAT was identified by the investigator prior to randomisation and included: ATG, ECP, MSCs, low-dose methotrexate, MMF, everolimus, sirolimus, etanercept or infliximab following institutional guidelines for dosing and administration. Treatment was to continue until a complete or partial response at which point immunosuppression was tapered down stepwise; tapering of ruxolitinib was permitted after day 56 of the study for patients with a treatment response. Standard allogeneic stem cell transplantation supportive care was allowed during the study and included: anti-infective medicinal products and transfusion support. Additionally, standard aGvHD prophylaxis and treatment medicinal products initiated before randomisation including systemic corticosteroids and calcineurin inhibitors such as ciclosporin or tacrolimus was permitted. Randomisation was stratified according to aGvHD grade (grade II versus grade III versus grade IV).
Primary outcome	Overall response rate (complete or partial response) at day 28 after randomisation, assessed by the investigator per MAGIC criteria. Defined as proportion of patients in each arm demonstrating complete response (score of 0 for grading in all evaluable organs) or partial response (improvement

	of 1 stage in ≥1 organs) compared with baseline organ staging without use of additional systemic therapies for aGvHD.
Secondary outcomes	• Durable overall response rate at day 56, assessed by the investigator per MAGIC criteria • Duration of response – evaluated in patients who achieved a CR or PR, at or before day 28 • Overall survival • Cumulative steroid dosing until day 56 • Failure-free survival - defined as relapse or progression of haematologic disease, non-relapse mortality or addition of another systemic treatment for aGvHD; the competing risk was the onset of cGvHD.
Statistical analysis	Efficacy analyses were carried out in the FAS, which included all patients to whom study treatment has been assigned by randomisation. A hierarchical statistical testing strategy was applied in the study for the primary outcome and durable overall response rate at day 56. Durable overall response rate at day 56 was only formally tested if the primary analysis of overall response rate at day 28 was statistically significant. Other secondary outcomes were not included in the hierarchical testing strategy, therefore the results reported for these outcomes are descriptive only and not inferential (no p-values reported).

aGvHD = acute graft versus host disease; ATG = anti-thymocyte globulin; BAT = best available therapy; CR = complete response; ECP = extracorporeal photopheresis; FAS = full analysis set; MAGIC = Mount Sinai aGvHD International Consortium; MMF = mycophenolate mofetil; MSCs = mesenchymal stem cells; PR = partial response

At the data cut-off for the primary analysis (25 July 2019), ruxolitinib treatment resulted in a statistically significant improvement in overall response rate at day 28 compared with best available therapy. Secondary outcomes including duration of response (DOR), overall survival (OS), cumulative steroid dosing at day 56 and failure-free survival were reported from the final analysis (data cut-off 23 April 2021).[11, 12]

Table 2.2: Primary and selected secondary outcome results from REACH2 in the FAS population.[11-13]

	Ruxolitinib (n=154)	**BAT (n=155)**
Primary outcome: investigator-assessed overall response rate at day 28 per MAGIC criteria[a]		
ORR at day 28, %)	62	39
Odds ratio (95% CI), p-value	2.64 (1.65 to 4.22), p<0.001	
CR, %	34	19
PR, %	28	20
Secondary outcome: investigator-assessed durable overall response rate at day 56 per MAGIC criteria[a]		
ORR at day 56,%	40	22
Odds ratio (95% CI), p-value	2.38 (1.43 to 3.94), p<0.001	
CR, %	27	16
PR, %	13	5.8
Secondary outcome: duration of response[b]		
Median DOR, days (range)	167 (22 to 677)	106 (10 to 526)
Secondary outcome: overall survival[b]		
Deaths, %	58	59
KM-estimated median OS, months	10.7	5.8 [c]
Hazard ratio (95% CI)	0.85 (0.63 to 1.14)	
Secondary outcome: cumulative steroid dosing until day 56		
Patients tapered off corticosteroids, %	22	15
Odds ratio (95% CI)	1.63 (0.91 to 2.92)	

BAT = best available therapy; CI = confidence interval; CR = complete response; DOR = duration of response; FFS = failure-free survival; KM = Kaplan-Meier; MAGIC = Mount Sinai aGvHD International Consortium; ORR = overall response rate; OS = overall survival; PR = partial response

[a] From the primary analysis data cut off (25 July 2019).

[b] OS data included 3 patients with longer follow-up data (up to 36 months).

[c] 49 patients in the BAT arm (32%) crossed over to the ruxolitinib arm. Adjustment was made to OS data following NICE technical support document 16. The adjusted median OS for the BAT arm was 5.25 months.

Patients in the best available therapy arm were permitted to crossover to receive ruxolitinib between day 28 and week 24 if they failed to meet the primary outcome or lost response thereafter, and did not have suspected cGvHD.

Failure-free survival (FFS) was a composite secondary outcome. The Kaplan-Meier estimated median FFS was 4.86 months in the ruxolitinib group and 1.02 months in the best available therapy group (HR: 0.51; 95% CI: 0.39 to 0.66). FFS was not adjusted for crossover.[13]

2.2. Health-related quality of life outcomes

Health-related Quality of Life (HRQoL) was assessed using two patient reported questionnaires: Functional Assessment of Cancer Therapy – Bone Marrow Transplant (FACT-BMT) and 5Q-5D-5L. Scores were measured at baseline, weekly for the first 2 months and then every 4 months thereafter until the end of treatment. There was an overall improvement in 5Q-5D-5L and FACT-BMT scores in both groups from baseline to week 24.[11, 12]

2.3. Supportive studies

REACH3 was an open-label, randomised, phase III study of ruxolitinib (n=165) compared with best available therapy (n=164) in patients ≥12 years with moderate or severe glucocorticoid refractory or dependant chronic GvHD (cGvHD) after allogenic stem cell transplantation. As described above, this submission relates only to acute GvHD (aGvHD). In the FAS population, there was a statistically significant improvement in ORR at week 24 of 50% for ruxolitinib and 26% for best available therapy (OR: 2.99; 95% CI: 1.86 to 4.80, p<0.001). Data from REACH3 on cGvHD health states and cGvHD disease-specific mortality were used to inform the economic case for this submission.[14]

The submitting company presented real world evidence to support the efficacy and safety of ruxolitinib. In a compassionate use programme for patients with steroid-resistant aGvHD (n=370) and cGvHD (n=775), 50% of aGvHD patients had grade III (severe) or grade IV (very severe) aGvHD at baseline. This reduced to 19% and 11% at the end of the initial supply (3 months) and first resupply of ruxolitinib (6 months), respectively; overall there was a best overall response of grade 0 (absence of aGvHD) or grade I (mild) in 56% of patients with aGvHD. In patients with aGvHD, corticosteroid use decreased from 91% at baseline to 64% during ruxolitinib treatment. [15]

*Other data were also assessed but remain confidential.**

3. Summary of Safety Evidence

In REACH2, the median duration of treatment in the ruxolitinib group was 63 days and in the best available therapy group was 29 days. Up to day 28, any treatment-emergent adverse event (AE) was reported by 95% (145/152) of patients in the ruxolitinib group and 93% (140/150) in the best available therapy group. Patients reporting a grade 3 or higher AE were 78% in both groups. In the ruxolitinib and best available therapy groups respectively, patients with a reported serious AE

were 38% versus 34%, patients with dose modifications were 38% versus 9% and patients discontinuing therapy due to an AE was 11% versus 5%.[11]

The most frequently reported treatment-emergent grade ≥3 AEs with an incidence ≥5% in either treatment arm were: thrombocytopenia (27% versus 15%), anaemia (22% versus 19%), platelet count decreased (14% versus 13%) and neutropenia (13% versus 9%).[11]

The submitting company also presented safety evidence from a longer treatment period (the end of the on-randomised treatment period) due to differences in the median duration of treatment in the ruxolitinib group compared with the best available therapy group. These results were generally consistent with the day 28 cut-off.

The regulator noted that the safety profile of ruxolitinib was generally similar to that previously reported, with a high incidence of dose adjustments and interruptions due to adverse events. Cytopenias and infections were described as the main safety risks. The regulator noted that these adverse events were manageable with dose modifications. See the SPC for further information.[1,11,12]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- In REACH2, at the primary analysis, compared with investigators choice of best available therapy, ruxolitinib was associated with a statistically significant improvement in the primary outcome, overall response rate at day 28; this was considered clinically relevant by the regulator.[12] A statistically significant improvement was also observed in the hierarchically tested secondary outcome, durable overall response rate at day 56.
- Secondary outcomes, including DOR, OS and cumulative steroid dosing at day 56 also numerically favoured ruxolitinib compared with best available therapy.[11]
- Ruxolitinib is the first licensed treatment for aGvHD in patients with an inadequate response to corticosteroids.

4.2. Key uncertainties

- The regulator noted that there is some uncertainty regarding the duration of benefit of ruxolitinib, as the overall response rate decreased between day 28 and day 56.[12]
- REACH2 had an open-label design because of the different routes of administration between treatment groups. This could introduce potential bias for subjective efficacy, safety and quality of life outcomes and these should be interpreted with caution.
- Patients in the best available therapy arm were permitted to crossover to ruxolitinib, this limits interpretation of survival outcomes. However, OS data was adjusted to account for crossover and this appears to be relatively consistent with the pre-planned FAS analysis.[11]
- REACH2 was a small study, and excluded patients with grade I aGvHD therefore there is uncertainty relating to clinical outcomes in this patient group. Patients had a variety of pre-existing severe medical conditions which could potentially impact the results.[11, 12]

- The real world evidence presented from the compassionate use programme had several limitations including confounding issues with patients on undisclosed concomitant medication and bias towards data gathering in patients who had a positive effect from ruxolitinib.[15]

4.3. Innovative Licensing and Access Pathway (ILAP)

The submitting company have advised that no further data are awaited from ongoing studies, therefore ruxolitinib is unsuitable for SMC interim acceptance.

4.4. Clinical expert input

Clinical experts consulted by SMC consider ruxolitinib to be a therapeutic advancement and that it fulfils an unmet need for this indication, as it represents the only licensed treatment option for the treatment of aGvHD in patients with an inadequate response to corticosteroids.

4.5. Service implications

No significant service implications are expected and the oral formulation of ruxolitinib may have benefits over some comparators.

5. Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of ruxolitinib, as an orphan equivalent and end of life medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Acute graft versus host disease (aGvHD) is a debilitating complication of allogenic stem cell transplantation and is associated with poor survival and quality of life. The mainstay of treatment is corticosteroids. Patients who do not respond to corticosteroids have limited treatment options, high mortality (80% to 90%), high morbidity, poor quality of life and an increased risk of progression to chronic GvHD.
- Acute GvHD can have a significant impact on patients' physical and emotional wellbeing. The symptoms associated with aGvHD can be distressing, challenging to manage and are associated with complications that requires frequent and prolonged hospital admissions. Acute GvHD can be stressful, traumatic, isolating and can place a financial burden on patients and their carers. Acute GvHD carries a significant care burden and places additional stress onto families and carers.
- PACE participants consider that there is an urgent and significant unmet need for an effective licensed treatment for aGvHD that does not respond to corticosteroids. There is no standard of care and currently available treatments are used off-label. Access to current treatments depends on geographical location and places significant time and financial strain on patients and carers.
- Ruxolitinib is an effective treatment for aGvHD, it significantly improves survival and quality of life compared with currently available treatments. It is administered orally and is convenient for patients, allowing them to be treated at home. The frequency and duration of hospital visits will be reduced, and treatment does not require intravenous access, thereby improving

psychological outcomes, quality of life and reducing the financial burden associated with current treatment options.

- Ruxolitinib also allows patients to reduce or discontinue therapies such as steroids and calcineurin inhibitors. Steroid dose reduction or cessation reduces the incidence of steroid induced side effects including distressing cushingoid body habitus, myopathy and hyperglycaemia. Reducing calcineurin inhibitors reduces the need for electrolyte replacement and avoids renal impairment, which can be severe and progressive. In addition, rarer complications related to calcineurin inhibitors, such as transplant associated microangiopathy, are more common in patients with severe GvHD.
- Ruxolitinib is generally well tolerated by patients compared with off-label treatments and side effects such as cytopenias are easily managed. As ruxolitinib is an oral medication, access to treatment would be equitable across Scotland.
- PACE participants agreed that the ruxolitinib should be used as per the licensed indication. Patients will be monitored and followed up by the transplant service and this is considered to be no more frequent than usual.

Additional Patient and Carer Involvement

We received a joint patient group submission from Anthony Nolan and Leukaemia Care, both organisations are registered charities. Anthony Nolan has received 0.01% pharmaceutical company funding in the past two years, with none from the submitting company. Leukaemia Care has received 9.48% pharmaceutical company funding in the past two years, with none from the submitting company. A representative from each of the patient groups participated in the PACE meeting. The key points of their joint submission have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company provided an economic case as described in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	Lifetime (51 years)
Population	Patients aged 12 years and older with aGvHD who have inadequate response to corticosteroids.
Comparators	Best available therapy (BAT) which included ECP, etanercept, infliximab, mycophenolate mofetil, mesenchymal stromal cells and sirolimus.
Model description	The model compared two treatment arms, ruxolitinib compared to BAT. The company utilised a Markov state-transition model with 7 discrete health states: aGvHD failure-free survival, aGvHD new systemic treatment (NST), aGvHD relapse of malignancy, cGvHD failure-free survival, cGvHD NST, cGvHD relapse of malignancy and an all-absorbing death state. Patients in each arm of the model entered in the aGvHD failure-free survival health state and had a chance each cycle to transition to relapse, aGvHD new systemic treatment or develop

	cGvHD. Patients in the aGvHD new systemic treatment health state could transition to the relapse or develop cGvHD. Patients in the model who developed cGvHD entered the cGvHD failure-free health state. Possible transition in the cGvHD health states were the same as for the respective aGvHD health states except that patients who had developed cGvHD could not develop aGvHD. The relapse health states represented a relapse of malignancy and so patients in these health states could only either remain in this health state or transition to the death health state. Patients in all health states could transition to the death state.
Clinical data	Comparative clinical efficacy in the economic evaluation was based on time-to-event data from REACH2 for failure-free survival. Failure in the analysis of REACH2 data comprised of relapse, addition of NST, or mortality prior to relapse or NST. Development of cGvHD was a competing risk. Median failure-free survival in the ruxolitinib arm (4.86 months) was statistically significantly longer than in the BAT arm (1.02 months). These data were crossover adjusted for the survival analysis. Clinical data for cGvHD in the model were from the REACH3 study.
Extrapolation	Transition probabilities in the model only varied by treatment arm from the aGvHD failure-free health state. The company used parametric survival modelling to extrapolate the crossover adjusted time to new systemic treatment, relapse and death from the Kaplan-Meier data from the respective treatment arms of REACH2. Distributions for extrapolations were selected based on statistical fit and clinical expert opinion. For transitions from failure-free to new systemic treatment the company selected independently fitted Gompertz distributions for ruxolitinib and BAT. The Generalised gamma distribution was fitted to time to relapse and death from REACH2 data for the respective treatment arms in the model for the transitions from the aGvHD failure-free health state. For the transition to cGvHD the company selected a single pooled model with a Generalised gamma distribution without a treatment effect. For the post-failure transitions in the aGvHD health states the company pooled crossover corrected data from both treatment arms of REACH2 and fitted parametric curves with the best statistical fit. Transition probabilities in the cGvHD health states were based on parametric survival modelling using time-to-event data from the BAT arm of the REACH3 study selecting curves according to statistical fit and clinical expert opinion.
Quality of life	Health state utilities were estimated using a mixed effects linear model for repeated measures fitted to EQ-5D data collected during the REACH2 and REACH3 studies from patients with aGvHD and cGvHD. Data from these studies were pooled and a single model was used. The company noted that failure-free utility improved over time, stabilising after Cycle 4 and so was included as a covariate in the utility model. This resulted in utility values in the first four cycles in the failure-free health state of 0.518 which increased to 0.677 after four cycles. Patients with aGvHD who started a new systemic treatment were applied a utility weight of 0.429. Patients with cGvHD and were failure-free had a utility weight of 0.689 and 0.673 if they transitioned to cGvHD new systemic treatment. Utility in the relapse health state (0.479) was from the literature.
Costs and resource use	Costs included covered medicine acquisition, management of adverse events, subsequent treatment costs, monitoring costs and health care resource use costs. Costs were not included for concomitant corticosteroid use nor for treatment administration as medicines were either

	oral or the cost of administration was assumed to be captured in the cost of the initial hospitalisation or in the overall procedure cost in the case of ECP.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price.

6.2. Results

Table 6.2: Base case results (PAS price for ruxolitinib)

Treatment	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
BAT	86,077	2.59	1.31	–	–	–	–
Ruxolitinib	CIC	3.61	CIC	CIC	1.03	CIC	36,698

Abbreviations: BAT = best available therapy; CIC = commercial in confidence; ICER = incremental cost-effectiveness ratio; LYG = life year gain; QALY = quality-adjusted life year

6.3. Sensitivity analyses

Table 6.3 Selected scenario analysis results (PAS price for ruxolitinib)

#	Parameter	Base case	Scenario	ICER (£/QALY)
1	Approach to REACH2 crossover	Crossover adjustment of REACH2 data included	Naïve analysis of REACH2 data	36,563
2	Treatment waning	No treatment waning	Treatment waning after Year 3	36,697
3	aGvHD transitions from the failure-free health state	to NST: ruxolitinib: Gompertz BAT: Gompertz	Ruxolitinib: Generalised gamma BAT: Gompertz	36,767
4		to relapse: ruxolitinib: Gen. gamma BAT: Gen. gamma	Ruxolitinib and BAT: log-normal fitted to pooled treatment arm data	35,358
5		to death: ruxolitinib: Gen gamma BAT: Gen. gamma	Ruxolitinib and BAT: generalised gamma fitted to pooled treatment arm data	33,753
6		to cGvHD: ruxolitinib and BAT: generalised gamma fitted to pooled treatment arm data	Ruxolitinib: Gen. gamma BAT: Gen. gamma	39,767
7	Utilities	Utility model combining data for patients with aGvHD and cGvHD from REACH2 and REACH3 with no subject level random effects, without relapse patients for health state utilities	Utility analysis conducted separately for aGvHD and cGvHD	39,888
8	aGvHD 2L treatments	aGvHD subsequent treatment distribution according to pooled BAT and ruxolitinib treatment arms 2L BAT	aGvHD subsequent treatment distribution according to respective treatment arms of REACH2	37,641
9	Combined scenarios		**3 + 4 + 5 + 6**	34,640

		Combining alternative assumptions for extrapolations for transition probabilities	
10		**9 + 7** Alternative extrapolations + alternative approach to estimating health state utilities	36,910
11		**10 + 8**	38,982
12	Cost-utility analysis	Cost-minimisation analysis	ruxolitinib cost-saving

Abbreviations: 2L = second line; aGvHD = acute graft versus host disease; BAT = best available therapy; cGvHD = chronic graft versus host disease; Gen. gamma = Generalised gamma; ICER= incremental cost-effectiveness ratio; incr. = incremental; NST = new systemic treatment; QALY = quality-adjusted life year

6.4. Key strengths

The strengths of the analysis were identified as being:

- Availability of randomised evidence from the REACH2 study to estimate transition probabilities in the economic evaluation.
- Availability of patient-level data from the BAT arm of REACH3 to inform disease trajectory in cGvHD in the model.

6.5. Key uncertainties

The analysis was associated with the following uncertainties:

- The company's choice to compare the relative clinical efficacy of ruxolitinib to BAT in the model using failure-free survival data from the REACH2 study and not to include data for response to treatment seemed uncertain. This approach did not capture the differences in survival and health outcomes that would seem likely to vary between responders and non-responders to treatment. The company argued that the approach taken more accurately captured disease trajectory than an approach based on response. Clinical experts consulted by SMC stated that the components of FFS were reflective of their clinical practice and clinically meaningful, so could be considered a surrogate for response.
- The open-label nature of REACH2 introduced a risk of bias to the time to NST results which was a key component of FFS and driver of the cost-effectiveness results. For instance, it seemed plausible that clinicians and patients could be more willing to delay time to next treatment in the intervention arm of the study in expectation of a better outcome compared to BAT. This uncertainty is compounded by patients in the BAT arm being able to switch to ruxolitinib which may have been viewed by patients and investigators as superior. This added a large degree of uncertainty to the results of the cost-effectiveness analysis. The company provided the results of a cost-minimisation analysis which assumed equal efficacy for ruxolitinib and BAT that suggested ruxolitinib was cost-saving (Scenario 12).

- The company's approach to extrapolating time-to-event data from REACH2 for the transition probabilities from the aGvHD failure-free health state seemed uncertain as it resulted in a median overall survival benefit for ruxolitinib compared to BAT that exceeded the non-statistically significant median overall survival benefit observed in REACH2. An alternative approach that involved assuming equal transitions for aGvHD failure-free to relapse (Scenario 4) and death (Scenario 5) and used the parametric curves with the best statistical fit for transitions to NST (Scenario 3) and cGvHD (Scenario 6) resulted in a lower estimate of cost-effectiveness when combined (Scenario 9).
- It seemed uncertain whether data from REACH3 were generalisable to the population in the economic model. In the REACH3 study only 53.7% of patients in the BAT arm had prior aGvHD and 10.4% of these had prior steroid-resistant aGvHD. This made the utility data, subsequent treatments and health outcomes in the cGvHD health states based on these data seem uncertain. Alternative plausible utility values were unavailable due to the paucity of data in this group of patients. Clinical expert advice indicated it was likely that patients with and without prior steroid-resistant aGvHD have similar quality of life and health outcomes if they developed cGvHD.
- Due to the heterogeneity between the study populations in the REACH2 and REACH3 studies the company's approach to combining these populations in a model to estimate health state utilities seemed uncertain. A scenario that adopted health state utilities from a model that analysed health-related quality of life data separately for these groups of patients resulted in higher estimate of cost effectiveness (Scenario 7).
- Basing subsequent treatments on data pooled across both treatment arms of REACH2 seemed uncertain and could feasibly bias the costs in favour of ruxolitinib if, for instance, patients in the BAT arm were less likely to receive the significantly more costly BAT treatments (mesenchymal stromal cells and ECP) at second line compared to patients in the ruxolitinib arm. A scenario that based subsequent treatment in each arm of the model on those observed in the respective treatment arms of REACH2 resulted in a higher estimate of cost effectiveness (Scenario 8).
- A scenario that combined a more conservative approach to estimating transition probabilities in the model with an alternative approach to utilities and using subsequent treatments in each model arm according to those observed in the respective treatment arm of REACH2 resulted in an ICER that was approximately 6% higher than the company's base case analysis (Scenario 11).

7. Conclusion

The Committee considered the benefits of ruxolitinib in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as ruxolitinib is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted ruxolitinib for use in NHSScotland.

8. Guidelines and Protocols

The British Committee for Standards in Haematology (BCSH) and the British Society for Bone Marrow Transplantation (BSBMT) published guideline Diagnosis and management of acute graft versus host disease in April 2012.[2]

The European Society for Blood and Marrow Transplantation (EBMT) published updated clinical practice recommendations Prophylaxis and management of graft versus host disease after stem cell transplantation for haematological malignancies in February 2024.[9]

9. Additional Information

9.1. Product availability date

March 2022

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per 28 days (£)
ruxolitinib	**10 mg orally twice daily**	**2,856**

Costs from BNF online on 30 January 2025. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 14 March 2025.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.