SMC2634

ruxolitinib cream (Opzelura®)

Incyte Biosciences UK Ltd

05 April 2024

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

ruxolitinib (Opzelura®) is not recommended for use within NHSScotland.

Indication under review: for the treatment of non-segmental vitiligo (NSV) with facial involvement in adults and adolescents from 12 years of age.

In two randomised, double-blind phase III studies, there was significantly greater facial repigmentation following 24 weeks of treatment with ruxolitinib cream compared with vehicle cream in patients with non-segmental vitiligo.

The submitting company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Vice Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Ruxolitinib is a Janus Kinase (JAK) inhibitor with selectivity for JAK 1 and JAK2. It potently inhibits the expression of several immune mediators considered directly responsible for producing T-lymphocytes that cause melanocyte destruction in vitiligo, including interferon gamma, C-X-C motif chemokine ligand 10 and Granzyme B.[1, 2]

Ruxolitinib cream is the first medicine to receive a marketing authorisation for the treatment of vitiligo. The recommended dose is a thin layer of ruxolitinib cream applied twice daily to the depigmented skin areas up to a maximum of 10% of body surface area. No more than two tubes of 100 g per month should be used. Once satisfactory repigmentation is achieved, treatment in those areas can be stopped. If depigmentation recurs after treatment discontinuation, therapy can be reinitiated on the affected areas.[1]

1.2. Disease background

Vitiligo is an auto-immune condition that is characterised by depigmented patches of skin due to a loss of melanocytes caused by T-cells. It is thought to affect 0.5 to 1% of the worldwide population. The extent of affected skin can range from limited or focal disease to almost complete pigment loss. Non-segmental vitiligo is the most common type occurring in up to 90% of cases and is characterised by asymptomatic, generalised, usually symmetrical, patches. These can affect various parts of the body but often begin on the face, genitals, fingers and hands. Although it is not life-threatening, vitiligo can have a substantial impact on a patient's quality of life and self-esteem.[2, 3]

1.3. Company proposed position

The submitting company has requested that ruxolitinib is restricted for use in patients for whom the disease has not responded to the off-label use of topical corticosteroids or topical calcineurin inhibitors or for whom off-label topical corticosteroids or topical calcineurin inhibitors are contraindicated, not tolerated or otherwise medically inadvisable.

1.4. Treatment pathway and relevant comparators

The treatment of vitiligo, when used, aims to improve the appearance of the skin. Psychological therapies (self-help or referral) and supplementary therapies, including sun protection, vitamin D supplementation and camouflage therapy, should be considered. There are no other medicines specifically licensed for vitiligo and treatment options, such as topical calcineurin inhibitors or topical corticosteroids, are used off-label. Current British guidelines recommend potent or very potent topical corticosteroids as a first-line treatment with consideration for topical tacrolimus (a calcineurin inhibitor) as an alternative for patients with facial vitiligo; an intermittent regimen of on-off topical corticosteroid or alternating weekly regimen of topical corticosteroid with topical tacrolimus can also be considered. Narrow-band ultraviolet B (NB-UVB) therapy is recommended for first-line phototherapy in patients with vitiligo that has not responded adequately to topical therapy and for those with extensive or progressive disease, but its use is limited by availability and the lengthy duration of treatment. In patients with rapidly progressive vitiligo, oral betamethasone can be considered. Surgery, including cellular grafting, and depigmenting

treatments can be considered for patients with stable, segmental or non-segmental vitiligo unresponsive to other treatments, but in need of further treatment.[3]

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of ruxolitinib cream for non-segmental vitiligo comes from two identical phase III studies (TRuE-V1 and TRuE-V2).[4]

Table 2.1. Overview of relevant studies[2, 4]

Criteria	TRuE-V1 and TRuE-V2
Study design	Two identical randomised, double-blind, phase III studies of 24 weeks followed by open-label extensions to week 52.
Eligible patients	- age ≥ 12 years - BMI, 17 to 40 kg/m^2 - clinical diagnosis of non-segmental vitiligo, with depigmented area including: - ≥ 0.5% BSA on the face - F-VASI score ≥ 0.5 - ≥ 3% BSA on non-facial areas - T-VASI score ≥ 3 - total body vitiligo area (facial and non-facial) ≤ 10%.
Treatments	Ruxolitinib cream or vehicle cream applied as a thin layer twice daily for 24 weeks to depigmented areas identified at baseline. At week 24, all patients could apply open-label, ruxolitinib cream twice daily for a further 28 weeks.
Randomisation	Patients were randomised in a 2:1 ratio, stratified according to geographical area (North America or Europe) and Fitzpatrick skin type (I [pale white] or II [white] versus III [light brown] to VI [deeply pigmented dark brown to black]).
Primary outcome	F-VASI75 response (defined as the proportion of patients who achieved ≥ 75% improvement from baseline in the F-VASI) at week 24. F-VASI is a tool for calculating the surface area of vitiligo depigmentation on the face.
Key secondary outcomes	- F-VASI50 response (defined as the proportion of patients who achieved ≥ 50% improvement from baseline in the F-VASI) at week 24 - F-VASI90 response (defined as the proportion of patients who achieved ≥ 90% improvement from baseline in the F-VASI) at week 24 - T-VASI50 response (defined as the proportion of patients who achieved ≥ 50% improvement from baseline in the T-VASI) at week 24 - VNS response (defined as a score of 4 [a lot less noticeable] or 5 [no longer noticeable]) at week 24 - Percentage change from baseline in facial BSA affected by vitiligo at week 24.
Statistical analysis	A hierarchical statistical testing strategy was applied to the primary and key secondary outcomes in the studies with no formal testing of outcomes after the first non-significant outcome in the hierarchy (ordered as above).

BMI = body mass index; BSA = body surface area; F-VASI = facial Vitiligo Area Scoring Index; T-VASI = total body Vitiligo Area Scoring Index; VNS = vitiligo noticeability scale

In TRuE-V1 and TRuE-V2, a significantly greater proportion of patients in the ruxolitinib cream groups compared with vehicle cream groups achieved a F-VASI75 response at week 24. There were also significant improvements in each of the key secondary outcomes at week 24 in both studies. Details are presented in Table 2.2, along with results for pooled analysis of both studies.

Table 2.2 Results for the primary and key secondary outcomes at week 24 in TRuE-V1, TRuE-V2 and in the pooled analysis[2, 4]

	TRuE-V1		TRuE-V2		Pooled analysis	
	Ruxolitinib (n=221)	Vehicle (n=109)	Ruxolitinib (n=222)	Vehicle (n=109)	Ruxolitinib (n=443)	Vehicle (n=218)
F-VASI75 response	30%	7.4%	31%	11%	31%	9.6%
Difference (95% CI)	22% (14 to 30) p<0.001		20% (11 to 28) p<0.001		21% (15 to 27)	
F-VASI50 response	51%	17%	51%	21%	52%	20%
Difference (95% CI)	34% (24 to 44) p<0.001		31% (20 to 41) p<0.001		32% (25 to 40)	
F-VASI90 response	15%	2.2%	16%	1.3%	16%	1.9%
Difference (95% CI)	13% (7.5 to 19) p=0.0038		15% (9.3 to 21) p=0.0065		14% (10 to 18)	
T-VASI50 response	21%	5.1%	24%	6.8%	22%	5.8%
Difference (95% CI)	16% (8.3 to 23) p=0.002		17% (9.5 to 25) p≤0.001		16% (11 to 21)	
VNS response	24%	3.3%	20%	4.9%	22%	4.2%
Difference (95% CI)	21% (14 to 28) p≤0.001		16% (8.5 to 23) p=0.0013		18% (13 to 23)	
Percentage change in F-BSA score	-29%	-9.5%	-26%	-7.0%	-28%	-7.9%
Difference (95% CI)	-19% (-27 to -12) p≤0.001		-20% (-29 to -10) p≤0.001		-20% (-26 to -14)	

F-VASI75 = ≥75% improvement in facial Vitiligo Area Scoring Index; CI = confidence interval; F-VASI50 = ≥50% improvement in facial Vitiligo Area Scoring Index; F-VASI90 = ≥90% improvement in facial Vitiligo Area Scoring Index; T-VASI50 = ≥50% improvement in total body Vitiligo Area Scoring Index; VNS = vitiligo noticeability scale; F-BSA = facial body surface area

Patients who completed the 24-week double-blind treatment periods could enter 28-week extensions, during which all patients received open-label ruxolitinib cream applied twice daily to week 52. At 24 weeks, 283 patients from TRuE-V1 entered the extension (193 from the ruxolitinib group and 90 from the vehicle group) and 308 patients from TRuE-V2 entered the extension (206 from the ruxolitinib group and 102 from the vehicle group). There were further improvements in the primary and key secondary outcomes between weeks 24 and 52.[1, 2]

2.2. Evidence to support the positioning proposed by the submitting company

On request, the company provided clinical evidence of post hoc analysis to support the proposed positioning. The evidence was from the group of patients in the pooled study population who had received any prior therapy (n=408). The proportion of patients achieving F-VASI75 was higher in the ruxolitinib cream group (n=272) compared with the vehicle cream group (n=136): 33% versus 9.6% respectively. The company also provided results for the group of patients in the pooled study population who had received prior topical corticosteroids or topical calcineurin inhibitors (n=307).

A F-VASI75 response was achieved in more patients in the ruxolitinib cream group (n=208) compared with the vehicle cream group (n=99): 35% versus 8.3% respectively.

Results have been published according to prior therapy for vitiligo that had been used by 62% of patients, including topical corticosteroids (28%), topical calcineurin inhibitors (32%) and phototherapy (32%). A F-VASI75 response at week 24 was achieved by:

- 32% (39/120) of ruxolitinib cream patients versus 9.1% (4/44) of vehicle cream patients who had received prior topical corticosteroids
- 32% (44/136) of ruxolitinib cream patients versus 6.5% (4/62) of vehicle cream patients who had received prior topical calcineurin inhibitors
- 34% (43/126) of ruxolitinib cream patients versus 7.8% (5/64) of vehicle cream patients who had received prior phototherapy.[2]

2.3. Health-related quality of life outcomes

Health Related Quality of Life (HRQoL) was assessed as a secondary outcome using the Dermatology Life Quality Index (DLQI) for adults and the Children's Dermatology Life Quality Index (CDLQI) for adolescents: (range 0 to 30 with higher scores indicating greater impact on quality of life). These instruments were used at baseline, week 12 and week 24.

Other exploratory outcomes included the facial and total body Physician Global Vitiligo Assessment (F-PhGVA and T-PhGVA), the facial and total body Patient Global Impression of Change (F-PaGIC and T-PaGIC), colour matching question, the Hospital Anxiety and Depression Scale (HADS), the Treatment Satisfaction Questionnaire for Medication (TSQM) and the Vitiligo-specific Quality of life instrument (VitQoL).

Results found no changes in DLQI and CDLQI over time. There were no differences between the groups for other outcomes with the exception of better treatment satisfaction in the ruxolitinib group compared with the vehicle group.[2]

2.4. Supportive studies

The TRuE-V LTE study was an extension study of TRuE-V1 and TRuE-V2, which comprised a further 52-week extension treatment period and a 4-week safety follow-up period. This study enrolled patients who had completed 52 weeks of treatment in the parent studies and included two cohorts depending on their F-VASI response.

In cohort A (withdrawal), 116 patients who had completed TRuE-V1 or V2 and achieved ≥F-VASI90 at week 52 were re-randomised in a double-blind manner to receive ruxolitinib or vehicle cream applied twice daily to 104 weeks. If relapse occurred (<F-VASI75 defined as a loss of 75% improvement from baseline at start of parent study), then patients received open-label ruxolitinib cream as a rescue treatment until the end of the study. The primary outcome was the time to relapse (<F-VASI75). At week 104, 15% of patients in the ruxolitinib group and 29% of patients in the vehicle group relapsed. In the vehicle group, nine of the 16 patients who relapsed did so within 4 months of stopping ruxolitinib cream. On retreatment with open-label ruxolitinib cream, 75% (12/16) patients regained a F-VASI75 response within a median of 12 weeks and 69% (11/16) a F-VASI90 response within 15 weeks.[1, 5]

In cohort B (extension), 342 patients who had completed TRuE-V1 or V2 and not achieved ≥F-VASI90 at week 52, continued to receive open-label ruxolitinib cream applied twice daily to 104 weeks. In those patients who had originally been randomised to ruxolitinib cream in the parent studies and had received 104 weeks of treatment, F-VASI75 response rate was 66% and F-VASI90 response rate was 34% at week 104.[1, 5]

2.5. Indirect evidence to support clinical and cost-effectiveness comparisons

The submitting company conducted an indirect treatment comparison (ITC) feasibility assessment but concluded that there was insufficient evidence to support an ITC to robustly compare the efficacy of ruxolitinib cream to existing off-label medicines (topical corticosteroids, topical calcineurin inhibitors and phototherapy).

3. Summary of Safety Evidence

In the pooled safety analysis of TRuE-V1 and TRuE-V2 at week 24 (end of vehicle-controlled treatment period), a treatment-emergent adverse event (AE) was reported by 48% (214/449) of patients in the ruxolitinib cream group and 35% (79/224) of patients in the vehicle cream group and these were considered treatment-related in 15% and 7.6% respectively. In the ruxolitinib and vehicle groups respectively, patients reporting a grade 3 or higher AE were 2.2% versus 1.8% (none of which were considered treatment-related) and patients with a reported serious AE were 1.8% versus 0.4%. Patients with a treatment interruption due to treatment emergent AEs were 1.3% versus 1.8% and patients discontinuing therapy due to an AE was 0.4% in both groups.[2]

The most frequently reported treatment-emergent AEs of any grade in the ruxolitinib cream group versus the vehicle cream group were: application site acne (5.8% versus 0.9%), application site pruritus (5.1% versus 2.7%), nasopharyngitis (4.2% versus 2.2%), headache (3.8% versus 2.7%), COVID-19 (2.9% versus 2.7%), upper respiratory tract infection (2.9% versus 2.2%), and sinusitis (2.2% versus 2.2%).[2]

Results from the 28 week extension phase to week 52 were similar.[2]

The SPC notes that non-melanoma skin cancers, predominantly basal cell carcinomas, have been reported in patients treated with topical ruxolitinib. However, most patients had risk factors, including prior phototherapy or prior non-melanoma skin cancers and a causal relationship has not been established. Periodic skin examination is recommended for all patients treated with ruxolitinib cream, particularly those with risk factors for skin cancer.[1]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- In two randomised, double-blind, phase III studies, there was significantly more patients with facial repigmentation, assessed by F-VASI75, when treated with ruxolitinib cream compared with vehicle cream. The F-VASI75 was specifically developed by the company to assess ruxolitinib cream in vitiligo studies and may not be used in clinical practice. It was based on the VASI, which is a validated physician-based assessment tool to quantify the depigmentation of vitiligo and is a composite estimate of the BSA of vitiligo patches and the degree of

repigmentation within these patches over time. An improvement of ≥ 75% in F-VASI was considered a clinically relevant change by the regulator.[2, 4]

- Results for this primary outcome were supported by significant improvements in all key secondary outcomes, including patient-reported improvement assessed by VNS response.[2, 4]
- Longer term treatment has indicated that there are further treatment improvements after week 24 and up to 104 weeks. However, patients who achieved an improvement of < 25% in F-VASI by week 52 were considered to be unlikely to show later clinically meaningful improvement and the SPC recommends that discontinuation should be considered.[1, 2]

4.2. Key uncertainties

- The vehicle-controlled study periods were limited to 24 weeks and the primary and key secondary outcomes were assessed at this timepoint. This was considered potentially too short a duration to reach full repigmentation. Further data to weeks 52 and 104 are available for patients initially randomised to ruxolitinib, which indicate that improvements were continued or maintained, but these are uncontrolled. With no data beyond 2 years, there is uncertainty over the longer term efficacy and safety of ruxolitinib cream.[2]
- The submitting company has proposed that ruxolitinib cream is restricted for use in patients for whom the disease has not responded to topical corticosteroids or topical calcineurin inhibitors or for whom topical corticosteroids or topical calcineurin inhibitors are contraindicated, not tolerated or otherwise medically inadvisable. The evidence provided by the company to support this positioning comes from post hoc analysis of patients who had received any prior treatment for vitiligo, the majority of whom had discontinued due to lack of efficacy.
- The company suggests that ruxolitinib cream is anticipated to be positioned as a step change between first-line (topical corticosteroids and topical calcineurin inhibitor) and second-line (phototherapy) options. This appears to be based on the place in therapy where the company considers that ruxolitinib cream provides the most clinical benefit for patients with the highest unmet need. The company considered that vehicle cream is the most relevant comparator. However, if a patient does not respond to topical corticosteroids and topical calcineurin inhibitors, they may move on to receive phototherapy, if available, rather than receive no active treatment (vehicle cream) in clinical practice.
- There are no direct or indirect data to compare ruxolitinib cream with other treatment options for vitiligo, so its relative efficacy and safety is unknown. Following an ITC feasibility assessment, the submitting company's conclusion of insufficient evidence to support a robust ITC seems reasonable. There are also no data on the use of ruxolitinib cream in combination with other medicines used to treat vitiligo.
- Despite the improvements in repigmentation, there were similar results in the ruxolitinib and vehicle groups for quality of life outcomes (DLQI, CDLQI, VitiQol and HADS); this was potentially due to low scores for these assessments at baseline.[2]

- Ruxolitinib cream is licensed for use in adults and adolescents aged over 12 years. In the TRuE-V1 and TRuE-V2 studies, only 11% (72/661) of patients were adolescents and the efficacy and safety appeared similar to adults.[2]
- In the TRuE-V1 and TRuE-V2 studies, the majority (82% [542/661]) of patients were white and 89% (590/661) had Fitzpatrick skin types II, III or IV. Subgroup analysis according to stratified skin type (I or II versus III to VI) found similar F-VASI75 response rates. However, the pooled study population included only 31 black or African American patients and 28 Asian patients and study results may be less generalisable patients in whom vitiligo may be more noticeable and more difficult to cover.[2]

4.3. Clinical expert input

Clinical experts consulted by SMC considered that ruxolitinib cream fills an unmet need in this therapeutic area and is a therapeutic advancement by offering an effective licensed treatment option.

4.4. Service implications

There may be an increase in the number of patients receiving treatment for vitiligo if a licensed treatment is available, which may have service implications including for follow-up.

5. Summary of Patient and Carer Involvement

The following information reflects the views of the specified Patient Group.

- We received a patient group submission from The Vitiligo Society, which is a registered charity.
- The Vitiligo Society has received 25% pharmaceutical company funding in the past two years, including from the submitting company.
- People with vitiligo experience a range of physical and psychological symptoms as a result of the condition. People describe feelings of isolation, sadness, frustration, stress, worry, difficulty in relationships, depression, anxiety, and feelings of insecurity and self-consciousness about how their skin looks. Parents also report heightened anxiety as vitiligo affects children's confidence. Vitiligo also causes physical discomfort such as sensitivity to sunlight and potential co-morbidities.
- Some patients described to the patient group that to them the diagnosis phase can seem like a lot of trial-and-error. Others feel like there are not any effective treatments available for vitiligo currently. For many of those that do experience repigmentation via the available treatment methods, this is rarely permanent or wholly effective.
- The patient group described how this new treatment represents hope for many people affected by vitiligo – they recognise that whilst it may not be a cure and it won't alleviate all the social, psychological and physical impacts of vitiligo, it does have the potential to lessen these impacts and enable people to live with more confidence.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

A summary of the economic analysis for ruxolitinib cream is provided in Table 6.1

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	Lifetime
Population	Adults and adolescents with non-segmental vitiligo (NSV) with facial involvement in adults and adolescents from 12 years of age. The company was seeking a position within the licence of patients for whom the disease has not responded to topical corticosteroids (TCS) or topical calcineurin inhibitors (TCI), or for whom TCS or TCI are contraindicated, not tolerated or are otherwise medically inadvisable.
Comparators	Vehicle cream/ no active treatment
Model description	Markov model with health states for initial treatment period, maintenance period, stable, retreated, stable retreated, non-response and dead.
Clinical data	The pooled TRuE-V1 and V2 studies provided response data for the first 24 weeks, and the TRuE V-LTE study up to 104 weeks provided evidence for maintenance period state for responders and transitions to the retreated state. Data for the base case of the model were from prior therapy sub-groups of the TRuE studies to reflect the positioning sought for ruxolitinib. These patients had previously received TCS, TCI, phototherapy and other therapies and represented 61% of the whole pooled population. Data from Cohort A of the TRuE V-LTE study were used to estimate sustained response and relapse probabilities, and Cohort B for the probability of not regaining response in the retreated state. Discontinuations for other reasons were also included in the economic analysis based on TRuE study data, and were higher for vehicle cream.
Extrapolation	Patients were assumed to receive treatment with ruxolitinib cream or vehicle cream for 24 weeks and then receive assessment for response. If not achieving an F-VASI75 response patients stopped treatment and moved to the non-response state, where they were assumed to receive best supportive care (BSC), consisting of vitamin D, cosmetic therapies, and phototherapy (narrow band [NB]-UVB) for a period of 10 years. Extrapolation beyond the TRuE V-1 and 2 pooled RCT evidence consisted of patients who achieved a F-VASI75 response continuing treatment in the maintenance period state but stopping treatment and moving to a stable state if a sustained response was achieved at 52 weeks. Sustained response was defined as F-VASI90 at week 52 following F-VASI90 at week 24. In addition, in a subsequent model modification to fix an inconsistency in the transition probabilities a one-off transition to sustained response for patients with F-VASI75-89 at week 24 who were F-VASI90 at week 52 was applied. Patients not meeting the sustained response criterion at 52 weeks were assessed for sustained response or non-response in 4 weekly cycles after. Patients in the stable state who then lost response (relapsed with F-VASI<75) were re-treated, and moved to the stable retreated state if regaining a F-VASI90 response. Patients could transition to non-response from the maintenance state and from the retreated

	state if not achieving a F-VASI90 sustained response, or from stable re-treated if lose response and relapse (F-VASI75). As after 24 weeks data from the LTE study to populate transitions in the model were only available for either ruxolitinib or vehicle cream, the same probabilities were assumed for each treatment arm (i.e. assumes no treatment effect for ruxolitinib vs vehicle cream.
Quality of life	Utilities were estimated via a mapping of the F-VASI to the EQ 5D-5L based on published algorithms in vitiligo (which mapped various vitiligo measures with the EQ 5D-5L and then converted to utilities by applying a cross-walking function to the 3L).[6] The published study did not directly use the F-VASI, but performed mapping using the Repigmentation Score (RPS) which the company assumed to be a proxy for the F-VASI. Mapping was also performed with the Vitiligo Noticeability Scale (VNS) in Begum et al[7] (close second best fitting model to RPS), and this was also applied by the company to estimate EQ 5D utilities in scenario analysis. The base case utilities used in the economic analysis were: 0.879 at baseline, +0.066 for F-VASI90 response, +0.056 for F-VASI75 response, +0.01 for F-VASI50 response, and -0.082 for non-response. Estimates of pigmentation loss in patients experiencing depigmentation were truncated, with an upper limit of -37.5% applied in the base case (as it aligned with mean observed loss across arms in the TRuE studies). Lowering the upper truncation limit impacted on reducing the disutility estimate for non-response. No disutilities were estimated for adverse events (AEs).
Costs and resource use	A medicine acquisition cost for ruxolitinib was estimated. A daily dose of 4.03g day was estimated for both ruxolitinib and the comparator, based on the median dose across treatment arms in the TRuE-V whole population data. Costs were also included for concomitant medications (vitamin D supplements, sunscreen, cosmetic therapies) received alongside ruxolitinib and vehicle cream in the initial period, maintenance period and retreated state. BSC costs incurred in the non-response state assumed for a period of 10 years consisted of the same therapies as concomitant therapies, but with the addition of phototherapy (NB-UVB provided on an outpatient basis for 3 sessions per week for 9 months of each year, repeated annually). The proportion of patients assumed to receive phototherapy was derived from UK vitiligo patients in an international observational study conducted by the company (VALIENT). Healthcare resource use costs were estimated by health state for disease management (consisting of GP consultations, outpatient consultations with dermatologists and visits for psychological support), assumed also to be received for a period of 10 years. Disease management resource use was highest in the non-response state. Costs were also estimated for selected AEs.
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

The base case results with the PAS indicated that ruxolitinib cream was dominant over vehicle cream (lower costs, greater health outcomes). Over the time horizon of the model, patients treated with ruxolitinib spent an additional 0.627 years in the F-VASI90 health state compared to the comparator.

The key driver of incremental cost was the additional medicines acquisition cost of ruxolitinib in both the initial period state and subsequent health states. The quality adjusted life year (QALY) benefits of ruxolitinib are driven by better 24 week F-VASI75 and F-VASI90 response rates vs. the comparator. This leads to longer time in the stable states due to sustained response (where also stop treatment reducing ruxolitinib drug costs), and cost offsets associated lower BSC and disease management costs associated with the non-response state.

6.3. Sensitivity analyses

Sensitivity analysis was performed varying parameters by ±20%, with the most sensitive variables being F-VASI75-89 response rate variation for vehicle cream/ no active treatment in the initial treatment state, F-VASI90 response rate variation for ruxolitinib cream in the initial treatment state, discontinuation of vehicle cream in maintenance phase NB-UVB hospital sessions per course, proportion receiving NB-UVB, FVASI90 for vehicle cream week 24. Ruxolitinib remained dominant across the range of sensitivity analyses presented by the company.

Table 6.2 shows the results for selected scenario analyses performed and presented in the submission, showing sensitivity to the approach to utility estimation (scenarios 3 and 4), the time for which BSC is assumed to be received (scenarios 5 and 6), and improved results in the sub-group Fitzpatrick skin type IV-VI (scenario 7). While all results still remained dominant, there was significant variation in the incremental costs and incremental QALYs underpinning the dominance result in some scenarios.

Table 6.2: Selected scenario analyses performed, with PAS

	Parameter	**Base case**	**Scenario**	**ICER (£/QALY)**
	Base case			Dominant
1	Time horizon	64 years	10 years	Dominant
2	Patient population form the pooled TRuE-V1&2 studies	Prior-therapy sub-group	Whole population	Dominant
3	Utility data source: depigmentation truncation	F-VASI DP -37.5%	F-VASI DP: -25%	Dominant
4	Utility mapping algorithm: VNS	Based on RPS as proxy for F-VASI	Using VNS algorithm	Dominant
5	Duration of BSC costs incurred in non-response state	10 years	5 years	Dominant
6	Duration of BSC costs incurred in non-response state	10 years	Lifetime	Dominant

7	Sub-group analysis TRuE-V studies	Prior therapy sub-group	Fitzpatrick skin type IV-VI	Dominant

Abbreviations: BSC= best supportive care; DP= Depigmentation; F-VASI= Facial Vitiligo Area Scoring Index; ICER= incremental cost-effectiveness ratio; QALY=Quality Adjusted Life Year; RPS= Repigmentation Score; VNS= vitiligo noticeability scale. Dominant= Ruxolitinib was estimated as having lower costs and greater health outcomes than the comparator.

Following the New Drugs Committee (NDC) meeting additional analyses were requested to explore combined uncertainties in the economic analysis with a simplified clinical pathway and potentially more plausible assumptions for key parameters relating to resource use assumptions. Additionally, analyses were requested to explore further cost-effectiveness in the Fitzpatrick type IV-VI sub-group as well as scenarios for assuming a lower daily dose of ruxolitinib for facial use only (rather than face and body which the base case dose estimate is based on). A description of these additional scenario analysis with PAS is presented in Table 6.3. The results from these additional scenario analyses moved from the base case dominance result to significantly increased cost per-QALYs. The company has requested that these results are not presented as they are considered commercial in confidence.

Table 6.3 Additional post NDC scenario analyses, with PAS

	Parameter	**Base case**	**Scenario**
	Base case		
8 a	**<u>Combined analysis:</u>** Retreatment on relapse from SR; Stop treatment with SR; Phototherapy use non-response BSC; Dermatologist/ psychosocial support outpatient visits Daily dose ruxolitinib	 Yes Yes VALIENT % for 10 years 0.419/1.38 visits per 4 weeks* 4.03g/day (median)	 No No 10% for 1 year Reduced 50% across all states 4.53g (mean est. dose)
8 b	8a+ F-VASI criteria for 24 week initial response assessment	8a + F-VASI75 criteria applied	8a +F-VASI50 criteria applied
8 c	8a+ alternative daily dose assumption for ruxolitinib	As 8a	8a with mean dose of 3.84g/day (log normal distribution analysis)
9 a	8a+Sub-group analysis TRuE-V studies	8a+Prior therapy population	8a+Fitzpatrick type IV-VI sub-group
9 b	8b+Sub-group analysis TRuE-V studies	8b+Prior therapy population	8b+Fitzpatrick type IV-VI sub-group + 8b
9 c	8c+Sub-group analysis TRuE-V studies	8c+Prior therapy population	Fitzpatrick type IV-VI sub-group + 8c
10 a	8a+Mean ruxolitinib dose estimated for the face only	As 8a	Estimated mean dose of 0.63g in prior therapy population
10 b	8a+ Mean ruxolitinib dose estimated for the face only	As 8a	Estimated mean dose of 0.63g in Fitzpatrick IV-VI sub-group

Abbreviations: BSC= best supportive care. F-VASI= Facial Vitiligo Area Scoring Index; ICER= incremental cost-effectiveness ratio; QALY=Quality Adjusted Life Year; SR= Sustained Response

6.4. Key strengths

- Clinical data for up to 104 weeks available to populate the economic model.
- Useful range of scenario analyses presented.

6.5. Key uncertainties

- Based on SMC clinical expert feedback the proportion of patients expected to receive phototherapy as part of non-response BSC is overestimated given the low availability of and access to phototherapy in Scotland. The company assumed patients would receive three sessions of NB-UVB per week for 9 months of the year for 10 years, which is far higher than would be expected based on SMC clinical expert feedback. The cost-effectiveness results were sensitive to assumptions regarding a lower use of phototherapy in actual clinical practice (see Table 6.3).
- Disease management costs (healthcare professional consultations), which are higher in the non-response state and hence higher for the comparator, are likely to be overestimated over the long term in particular for dermatologist consultations and outpatient visits for psychological support. This was explored further as part of requested combined scenario analysis, with an upward impact on the ICER (see Table 6.3).
- The utility in the non-response state was estimated from the base case mapping approach to result in a decrement from baseline. This implies that BSC including phototherapy is ineffective, which has questionable clinical plausibility. An exploratory scenario analysis assuming no disutility was requested (as a proxy for phototherapy having some potential benefit within the BSC mix) but not provided, but would increase the ICER from the base case. It is noted that the alternative mapping approaches investigated by the company either had a much smaller decrement associated with the non- response state (table 6.2 scenario 3) or did not result in any decrement associated with the non-response state (table 6.2 scenario 4).
- While the inclusion of a wider measurement of sustained response is a reasonable modification for the model design submitted, other limitations with the complexity and clinical plausibility of the model health states and transitions means there is high uncertainty in the ability of the current model to be able to adequately assess the cost-effectiveness of ruxolitinib cream. These include applying a F-VASI 75% improvement criteria at 24 weeks for assessing non-response when in the TRuE-V studies patients could continue treatment without achieving this level of response. Hence, the proportion of patients ceasing ruxolitinib treatment at 24 weeks (and not incurring medicines costs) maybe overestimated. Using F-VASI50 response criteria instead was explored further in the requested combined scenario analysis, with an upward impact on the ICER (see Table 6.3).
- In addition, there is uncertainty that the model will reflect clinical practice reality beyond the maintenance phase. For instance, based on SMC clinical expert feedback it is uncertain if in clinical practice treatment would be stopped with F-VASI90 response in the maintenance phase, or that retreatment would be likely in these patients with future loss

of response (the model also assumes stopping and restarting treatment with vehicle cream which lacks plausibility). This was explored further as part of requested combined scenario analysis, with an upward impact on the ICER (see Table 6.3).

- The F-VASI does not seem to be used as an assessment measure in clinical practice. SMC clinical expert feedback was that vitiligo response assessment would include use of photographic evidence, judgement, DLQI, so there is uncertainty as to whether the response assessment and outcomes included in the economic model will be representative of clinical practice.
- The dose of ruxolitinib is based on a median daily dose for ruxolitinib plus vehicle cream from the whole pooled TRuE-V population. Mean dose is more appropriate to use. By using daily dose no account has been taken of possible tube wastage, in particular at 24 weeks assessment when a high proportion of patients are assumed to cease treatment due to non-response. Further scenario analysis was requested from the company to use mean doses and include possible wastage. The company provided alternative approaches to estimation of mean dose including using observed data from the TruE-V studies but excluding 9 outliers who had very high doses, or using a log normal distribution analysis with wastage accounted for. The former approach resulted in a higher daily dose than in the base case (4.53g) and so increased the ICER and the latter led to lower doses (3.84g) producing a lower ICER. The appropriate dose to use was explored further as part of requested combined scenario analysis (see Table 6.3).
- Phototherapy has not been included as a comparator on the grounds that there is low availability in Scotland. This was confirmed by SMC clinical experts, but it is uncertain whether it should be a comparator at least for a small proportion of patients.
- Further scenario analysis assuming a lower estimated dose of 0.63g day for use of ruxolitinib based on restricting use to the face only (which would align with F-VASI outcomes) resulted in much lower ICERs (Scenarios 10a and b, Table 6.3).
- Overall, there were multiple uncertainties in the economic modelling, which means the base case is likely to be too optimistic and scenario analysis results in Table 6.2 and 6.3 are highly uncertain. Key uncertainties relate to: the clinical practice applicability of the response assessment criteria and the pathway beyond the maintenance state; the overestimates of the use of phototherapy within non-response BSC state and other costs of BSC and disease management that drives cost offsets; and the appropriate estimate of daily ruxolitinib dose to use. The post- NDC scenario analysis that was requested to explore a simplified clinical pathway and combined uncertainties in these key parameters resulted in high ICERs in the prior therapy population (Scenarios 8a-c, Table 6.3), and lower but still high ICERs in the Fitzpatrick type IV-VI sub-group (Scenarios 9a-c, Table 6.3). The results in Table 6.3 would also be sensitive to variation in approaches to estimation of health state utilities, but were not explored further.

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

7. Conclusion

After considering all the available evidence, the Committee was unable to accept ruxolitinib for use in NHSScotland.

8. Guidelines and Protocols

The British Association of Dermatologists published guidelines for the management of people with vitiligo in 2021.[3]

The International Vitiligo Task Force produced guidelines for the diagnosis, management, and treatment recommendations of vitiligo that were published in 2023.[8, 9]

9. Additional Information

9.1. Product availability date

23 January 2024

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
ruxolitinib cream	**applied to affected area twice daily**	**up to £15,768**

Costs from company submission and are based on up to a maximum recommended amount of two 100 g tubes of cream per month. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 380 patients eligible for treatment with ruxolitinib 1.5% cream in year one, rising to 1,896 by year five, to which confidential estimates of treatment uptake were applied.

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

References

1. Incyte Biosciences UK Ltd. Ruxolitinib 15 mg/g cream (Opzelura®) Summary of product characteristics. Electronics Medicines Compendium https://www.medicines.org.uk/. Last updated 13 November 2023.
2. European Medicines Agency (EMA). European Public Assessment Report. Ruxolitinib (Opzelura). 23/02/2023, EMEA/H/C/005843/0000. www.ema.europa.eu
3. Eleftheriadou V, Atkar R, Batchelor J, McDonald B, Novakovic L, Patel JV*, et al.* British Association of Dermatologists guidelines for the management of people with vitiligo 2021. Br J Dermatol. 2022;186(1):18-29. Epub 2021/06/24.
4. Rosmarin D, Passeron T, Pandya AG, Grimes P, Harris JE, Desai SR*, et al.* Two Phase 3, Randomized, Controlled Trials of Ruxolitinib Cream for Vitiligo. N Engl J Med. 2022;387:1445-55.
5. Clinical Trials. A double-blind, vehicle-controlled, randomized withdrawal and treatment extension study to assess the long-term efficacy and safety of ruxolitinib cream in participants with vitiligo NCT04530344, last updated 19 July 2023; available from: www.clinicaltrials.gov.
6. Begum ,R Crott R, Martina R, Louizidou EM, Khan I. Estimating Health Related Quality of Life Effects in Vitiligo. Mapping EQ-5D from vitiligo specific scales: VNS, VitiQoL and repigmentation measures using data from the Hi-Light Trial. Health and Quality of Life Outcomes (2023) 21:85
7. Begum R, Crott R, Martina R, Louizidou EM, Khan I. Estimating Health Related Quality of Life Effects in Vitiligo. Mapping EQ-5D from vitiligo specific scales: VNS, VitiQoL and re-pigmentation measures using data from the Hi-Light Trial. Health and Quality of Life Outcomes Journal (In Press). 2023.
8. Seneschal J, Speeckaert R, Taieb A, Wolkerstorfer A, Passeron T, Pandya AG et al. Worldwide expert recommendations for the diagnosis and management of vitiligo: position statement from the international Vitiligo Task Force - Part 2: specific treatment recommendations. J Eur Acad Dermatol Venereol 2023;37:2185-95.
9. van Geel N, Speeckaert R, Taïeb A, Ezzedine K, Lim HW, Pandya AG*, et al.* Worldwide expert recommendations for the diagnosis and management of vitiligo: Position statement from the International Vitiligo Task Force Part 1: towards a new management algorithm. J Eur Acad Dermatol Venereol. 2023;37(11):2173-84.

This assessment is based on data submitted by the applicant company up to and including 28 March 2024.

**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.