Single Technology Appraisal

Ruxolitinib for treating non-segmental vitiligo in people 12 years and over [ID3998]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ruxolitinib for treating non-segmental vitiligo in people 12 years and over [ID3998]

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance (DG) from Incyte**
   a. DG response
   b. Appendix A
   c. Appendix B

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. Vitiligo Society
   b. Vitiligo Support UK
   c. British Association of Dermatologists (BAD)
   d. British Dermatological Nursing Group (BDNG)

3. **Comments on the Draft Guidance from experts:**
   a. Pav Korpal – patient expert, nominated by Vitiligo Support UK
   b. Dr Viktoria Eleftheriadou – clinical expert, nominated by British Association of Dermatologists (BAD)

4. **Comments on the Draft Guidance received through the NICE website**

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 **External Assessment Group critique of company comments on the Draft Guidance**

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

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Ruxolitinib for treating non-segmental vitiligo in people 12 years and over [ID3998]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 21 February 2024. Please submit via NICE Docs.

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

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Disclosure Please disclose any funding received from the Company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the Company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Submitting Company – not applicable
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted] on behalf of Incyte Biosciences UK Ltd

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.

	Executive summary
	
	The company thanks NICE for appraising ruxolitinib 1.5% cream for the treatment of non-segmental vitiligo (NSV) with facial involvement in people aged 12 years and over and welcomes the opportunity to comment on the draft guidance. The company was disappointed to hear that ruxolitinib 1.5% cream was not recommended, particularly given the substantial burden of vitiligo on people and their quality of life and the current paucity of licensed treatment options. As the only licensed topical treatment option for NSV with facial involvement, ruxolitinib 1.5% cream is a truly innovative therapy which achieves notable improvements in repigmentation and thereby quality of life for people with NSV. Further, as noted by the committee during the appraisal, patients and clinicians would welcome ruxolitinib 1.5% cream as a treatment option for NSV with facial involvement.
	
	To further demonstrate that ruxolitinib 1.5% cream is cost-effective and deserving of a positive recommendation, the company has revised the PAS, presented new evidence and updated the cost-effectiveness analysis to align with the committee's preferences, as summarised below:
	
	• **Positioning (ACD Section 3.3):** The company acknowledges clinician agreement with the positioning of ruxolitinib 1.5% cream in the treatment pathway but wishes to clarify that ruxolitinib is being positioned as a secondary care treatment option.
	• **Comparators (ACD Section 3.4):** In response to the committee's request for comparative effectiveness evidence against phototherapy, the company has presented an unanchored matching-adjusted (weighted) indirect comparison (MAIC) using published data from the HI-Light study. Repigmentation scores (RPS) used in the HI-Light study and the facial vitiligo area scoring index (F-VASI) used in the TRuE-V studies were assumed equivalent measures of change in pigmentation from baseline. This comparison suggests that ruxolitinib 1.5% cream has 7 to 8 times higher odds of achieving response than narrowband ultraviolet B (NB-UVB) therapy in patients with vitiligo. The results from this MAIC were used to inform the comparison of ruxolitinib 1.5% cream with phototherapy in the cost-effectiveness model.
	• **Economic model and resource use (ACD Sections 3.7, 3.8, 3.10 and 3.11):** The company has updated the cost-effectiveness model to align with the committee's preferences. The key updates which are expected to have a significant impact on the ICER are summarised below:
	  ○ **Response definitions:** Initial response is defined as F-VASI>25 (i.e., patients with at least 25% improvement in pigmentation are considered responders).
	  ○ **Structural assumptions:** All patients are eligible to transition to the stable health state. Further, retreatment assumptions were modified;

in the comparison with NB-UVB, patients do not receive NB-UVB in the non-response health state.
- **Costs and resource use:** Cost and resource use assumptions were revised.
- **Dosing:** The dosing assumption for the base case was updated to use the mean daily dose of ruxolitinib cream from the pooled TRuE-V studies after using appropriate methods to account for missing data.

The revised model includes multiple conservative estimates which are worth consideration. Firstly, the base case assumed a dose of ruxolitinib 1.5% cream of 3.84 g/day, based on mean values of ruxolitinib cream calculated from the pooled TRuE-V studies. In contrast, real-world evidence from multiple sources suggests the mean usage of ruxolitinib 1.5% cream in clinical practice is expected to range between [redacted] to [redacted]. Further, the base case estimates that patients will use 14 tubes of ruxolitinib 1.5% cream per year. In contrast, clinical expert feedback from a clinician in Germany who is treating patients with ruxolitinib 1.5% cream, suggests that patients on average will use 5 to 6 tubes of ruxolitinib 1.5% cream per year. Therefore, the dosing estimate used in the base care is very conservative compared to the expected usage in clinical practice, as informed by real-world evidence and clinical expert opinion. Of note, when the higher range from the real-world estimate of ruxolitinib 1.5% cream usage is used (2.23 g/day), the incremental cost-effectiveness ratio (ICER) decreases by 42% from the base case.

Another conservative estimate in the model is that a cost of £0 is applied to no active treatment but efficacy outcomes from the vehicle arm of the TRuE-V trials is still applied. This results in a higher ICER compared with the more plausible scenario that no active treatment is assumed to have no treatment effect.

Table 1 summarises the updated cost-effectiveness analysis, which includes a revised PAS price. The revised cost-effectiveness model compares ruxolitinib 1.5% cream with no active treatment[i] (either followed by NB-UVB or not) and NB-UVB (either as monotherapy or in combination with topical corticosteroid [TCS]). Results demonstrate that, despite using conservative dosing and cost estimates, ruxolitinib 1.5% cream is dominant versus NB-UVB either as a monotherapy or in combination with TCS. Ruxolitinib 1.5% cream is also a cost-effective option versus no active treatment either when followed by NB-UVB or without any follow-up treatment. Further detail on the economic model methods and results can be found in Appendix A.

Table 1. Updated cost-effectiveness analysis results for ruxolitinib 1.5% cream (new PAS price)

	Ruxolitinib 1.5% cream versus NB-UVB	Ruxolitinib 1.5% cream versus NB-UVB + TCS	Ruxolitinib 1.5% cream versus no active treatment*	Ruxolitinib 1.5% cream versus no active treatment*

[i] The company have aligned terminology with that of the draft guidance; no active treatment is equivalent to vehicle cream.

Ruxolitinib for treating non-segmental vitiligo in people 12 years and over [ID3998]

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			followed by NB-UVB	
Incremental costs	[redacted]	[redacted]	[redacted]	[redacted]
Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]
Incremental time in F-VASI90	0.705	0.639	0.920	0.920
ICER	Dominant	Dominant	£18,103	£20,018

Abbreviations: F-VASI, facial vitiligo area scoring index; ICER, incremental cost-effectiveness ratio; NB-UVB, narrowband ultraviolet B; PAS, Patient Access Scheme, QALY, quality-adjusted life year; TCS, topical corticosteroid.
*The company have aligned terminology with that of the draft guidance; no active treatment is equivalent to vehicle cream

In summary, the company have made substantial efforts to drastically reduce the uncertainty surrounding the cost-effectiveness of ruxolitinib 1.5% cream. This includes a revised PAS, new indirect treatment comparisons and an updated cost-effectiveness model in accordance with the committee's preferences, which included very conservative estimates. The revised cost-effectiveness analysis maintains that ruxolitinib 1.5% cream is a cost-effective use of NHS resources and deserving of a positive recommendation. The company would also like to request that the committee consider the additional benefits of ruxolitinib cream that were not captured in the model, in line with precedence from the recent appraisal of ritlecitinib for treating alopecia areata (ID4007). This includes greater consideration of the limitations of the EQ-5D in capturing the quality of life impairment associated with vitiligo, as well as the innovative nature of ruxolitinib 1.5% cream as the only licensed treatment option for NSV that would be welcomed by clinicians and patients as a much-needed topical treatment option.

1	**Positioning of ruxolitinib 1.5% cream for the treatment of NSV with facial involvement in adults and adolescents from 12 years of age (response to committee comments in ACD Section 3.3)** The committee agreed with the company's proposed positioning of ruxolitinib 1.5% cream as a step-change therapy between existing first- and second-line treatments for NSV with facial involvement (i.e., after topical corticosteroids or topical calcineurin inhibitors, but before phototherapy), but was unsure of the treatment setting for the prescribing, supply and monitoring of ruxolitinib cream and whether this would implicate the current commercial arrangement. The Company would like to clarify that ruxolitinib cream is being positioned as a secondary care treatment option with an agreed Patient Access Scheme (PAS). Additionally, as noted by the committee, NHS England also anticipates that ruxolitinib cream will be prescribed, supplied and monitored in the secondary care setting.

	Ruxolitinib cream is a step-change in therapy for people with NSV with facial involvement, who are an underserved patient group due to the paucity of convenient and effective treatment options. The introduction of ruxolitinib cream in secondary care ensures fair access to an innovative and effective topical advanced treatment option for a historically overlooked condition. Furthermore, ruxolitinib cream should be initiated and supervised by physicians with experience in the diagnosis and treatment of non-segmental vitiligo, per the summary of product characteristics (SmPC). Although the company maintains its position of secondary care treatment initiation and prescribing, we will be open to also consider specific circumstances where shared care arrangements can be feasibly put in place, for example, where General Practitioners with Extended Roles (GPwER) provide ongoing treatment in primary care.
2	**Structural changes in the revised cost-effectiveness model (response to committee comments in ACD Section 3.7 and Section 3.8)** The model submitted by the company was a de novo model developed for a disease area which does not have precedent from prior appraisals. The company endeavoured to develop an appropriate and clinically relevant cost-effectiveness model, guided and validated by clinical experts who were also involved in the elicitation of some input parameters. However, the company understands that the committee considered the submitted cost-effectiveness model to be unsuitable for decision-making. The company is keen to reduce uncertainty in the model and has accepted the feedback provided by the committee. As such, the cost-effectiveness model has been extensively revised to address the structural concerns raised by the committee. Specifically, the following changes were implemented in the revised version of the model: • Initial response is defined as F-VASI25 at week 52 (i.e., patients achieving at least a 25% improvement in repigmentation are classed as responders). • Patients who achieve F-VASI90 at week 52 directly transition to stable health state. • Response is reassessed at week 104 (i.e., 2 years) as a one-off approach to align with the duration of the TRuE-V and long-term extension (LTE) studies and clinical practice. Patients who achieve F-VASI90 move to the stable state, patients with F-VASI<25 move to the non-response state and patients with F-VASI25-89 remain in the same health state (maintenance/retreatment period), where they stop treatment and gradually drop out to non-response over time. • There is an optional retreatment component (retreated and stable retreated health states) that patients can enter following relapse from stable state. This

Ruxolitinib for treating non-segmental vitiligo in people 12 years and over [ID3998]

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is to acknowledge the paucity of comparative data in the longer-term (i.e., beyond 9 months for NB-UVB and 6 months for no active treatment).

- A lifetime time horizon is applied to costs in the non-response health state.
- A direct comparison with phototherapy (i.e., NB-UVB either as monotherapy or in combination with TCS) is incorporated in the model (see Comments 3 and 4).
- 'Maintenance period' has been renamed to 'maintenance/retreatment period' to allow for the different treatment schedules anticipated between ruxolitinib cream (continuous treatment following initial response) and NB-UVB (retreatment following initial response after a 3-month off-treatment period).

Additionally, revisions have been made to assumptions on the dosing for ruxolitinib 1.5% cream (see Comment 6) and healthcare resource use and costs (see Comment 7). In line with the removal of a cost for vehicle cream, the vehicle cream is now referred to as 'no active treatment' in the model.

With the above modifications, the company believe that the revised model should be considered aligned with clinical practice and the proposed positioning of ruxolitinib cream as a second-line therapy, reflective of the natural history of vitiligo and an accurate representation of the data from the TRuE-V studies. For detailed information on the revision of the cost-effectiveness model, please refer to Appendix A.

3

Comparison of ruxolitinib 1.5% cream with phototherapy and no active treatment (response to committee comments in ACD Section 3.4)

Noting the committee's concerns on the uncertainty of the comparison between ruxolitinib cream and phototherapy, the company have presented a new indirect treatment comparison (ITC) between ruxolitinib 1.5% cream and NB-UVB +/- TCS (see Comment 4). The results were used to inform a cost-effectiveness analysis for ruxolitinib cream vs. NB-UVB using the revised model. **Table *2*** presents cost-effectiveness results for the comparison of ruxolitinib 1.5% cream with NB-UVB, which shows that ruxolitinib cream is less costly and more effective (i.e., dominant) compared to NB-UVB. Results for the comparison with NB-UVB+TCS therapy are available in **Table 1** and in Appendix A, which support the same conclusion.

Table 2. Base-case results of ruxolitinib 1.5% cream versus NB-UVB (new PAS price)

	Ruxolitinib 1.5% cream	NB-UVB
Costs	[redacted]	[redacted]
QALYs	[redacted]	[redacted]
Incremental costs	[redacted]	
Incremental QALYs	[redacted]	
ICER	Dominant	

Abbreviations: ICER, incremental cost-effectiveness ratio; NB-UVB, narrowband ultraviolet B; QALY, quality-adjusted life year.

Ruxolitinib for treating non-segmental vitiligo in people 12 years and over [ID3998]

Draft guidance comments form

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Table 3 Error! Reference source not found.presents the results from the submitted base case comparison of ruxolitinib 1.5% cream versus no active treatment followed by NB-UVB using the revised cost-effectiveness model. Ruxolitinib cream is cost-effective at the willingness-to-pay thresholds accepted by NICE. In line with the committee's preferences, this analysis includes the conservative assumption that 'no active treatment' is associated with zero costs but has the same efficacy as the vehicle arm of the TRuE-V trials. This results in a higher ICER compared with the more plausible scenario that no active treatment is assumed to have no treatment effect.

Table 3. Base-case results of ruxolitinib 1.5% cream versus no active treatment followed by NB-UVB (new PAS price)

	Ruxolitinib 1.5% cream	No active treatment followed by NB-UVB
Costs	[redacted]	[redacted]
QALYs	[redacted]	[redacted]
Incremental costs	[redacted]	
Incremental QALYs	[redacted]	
ICER	£18,103	

Abbreviations: ICER, incremental cost-effectiveness ratio; NB-UVB, narrowband ultraviolet B; QALY, quality-adjusted life year.

The committee also argued that a comparison of ruxolitinib cream with no active treatment would be reflective of patients in secondary care who are not eligible for phototherapy. Results for this are presented in **Table 1** and in Appendix A, which maintain that ruxolitinib 1.5% cream is cost-effective. However, the company feel that this scenario is not a fair representation of clinical practice as it is extremely conservative to assume that patients who do not go on to receive phototherapy will never receive any active treatment in their lifetime for their vitiligo, particularly if they have been referred to secondary care and considered for phototherapy. As the eligibility criteria for phototherapy is not well-established, the key contributing factors to patients with vitiligo not undergoing phototherapy can be assumed to be limited NHS resources and patient choice as opposed to a contraindication. As such, it is plausible that these patients will receive alternative off-label treatments (rather than no treatment), and a proportion of these patients may go on to receive phototherapy at a later date. Therefore, the company believe the ICER for ruxolitinib 1.5% cream versus no active treatment followed by NB-UVB is more plausible for patients who are not 'eligible' for phototherapy than a comparison of ruxolitinib 1.5% cream versus no active treatment.

In summary, after revising the cost-effectiveness model in line with the committee's preferred assumptions and model structure, the cost-effectiveness results demonstrate that ruxolitinib 1.5% cream is dominant versus NB-UVB either as a monotherapy or in combination with TCS. Ruxolitinib 1.5% cream is also a cost-effective option versus no active treatment either when followed by NB-UVB or without any follow-up treatment.

4	**Comparative effectiveness of ruxolitinib 1.5% cream versus NB-UVB therapy (response to committee comments in ACD Section 3.5)**

The Company has met the request from NICE to conduct an ITC of ruxolitinib 1.5% cream versus NB-UVB +/- TCS treatment, which was used to inform the cost-effectiveness comparison between the two therapies presented in Comment 3.

The methods and results of the ITC are reported in Appendix A. In summary, a naïve (unweighted) and a matching-adjusted (weighted) indirect comparison (MAIC) were conducted for the overall population. The HI-Light study was used to inform efficacy of NB-UVB[1] and the pooled TruE-V studies informed efficacy of ruxolitinib 1.5% cream. RPS used in the HI-Light study and F-VASI used in the TruE-V studies were assumed reasonably equivalent measures of change in repigmentation from baseline. For the MAIC, participants from the pooled TruE-V trials were matched to participants from the HI-Light trial on age, sex, and Fitzpatrick I-III, which were selected based on clinical input among the mutually reported baseline characteristics between the two clinical studies. Analyses were conducted at 6-month and 9-month timepoints for each of the following repigmentation response outcomes: 0-24% (non-responders); 25-100%; 50-100%; 75-100%. Odds ratios (ORs) and differences in proportions were estimated along with 95% confidence levels (CL) and p-values using a random effects model. Correlations were derived to understand the strength of the relationship between F-VASI and Total Body Vitiligo Area Scoring Index (T-VASI). Week 40 data inform the cost-effectiveness analysis.

<u>Comparison of Ruxolitinib 1.5% cream and NB-UVB (monotherapy) at 9 months (40 weeks)</u>

Table 4 presents the ORs from the week 40 MAIC analysis using data from the HI-Light and pooled TRuE-V studies. Patients treated with ruxolitinib 1.5% cream were statistically significantly more likely to achieve an overall response (25-100% repigmentation) compared to those treated with NB-UVB ([redacted]; p<0.001) after 9 months of treatment (Table 4).

Table 4. Modelled estimates (OR): F-VASI/RPS ruxolitinib 1.5% cream vs NB-UVB monotherapy at 9 months (Week 40)

Repigmentation Response/ Outcome (F-VASI)	Naïve estimates (unweighted) OR (SE) [95% CL; p-value] Rux 1.5% Cream vs NB-UVB	MAIC estimates (weighted) Odds Ratio (SE) [95% CL; p-value] Rux 1.5% Cream vs NB-UVB
0-24%	[redacted] **p<0.001]***	[redacted] **p<0.001]***
25-100%	[redacted]**; p<0.001]***	[redacted] **p<0.001]***
50-100%	[redacted] **p<0.001]***	[redacted] **p<0.001]***
75-100%	[redacted]**; p<0.001]***	[redacted] **p<0.001]***

Abbreviations: CL, confidence level; NB-UVB, narrowband ultraviolet B; Rux, ruxolitinib; SE, standard error.
*Statistically significant at the 2-sided 5% level.
Effective Sample Size (ESS) for ruxolitinib 1.5% Cream (vs NB-UVB) at week 40: 326.

Comparison of ruxolitinib 1.5% cream and NB-UVB + TCS (Combination Therapy) at 9 months (40 weeks)

In a comparison of ruxolitinib 1.5% cream with a combination therapy of NB-UVB + TCS, the OR of achieving at least 25% repigmentation was 5.74 ([redacted]; p<0.001) (**Table 5**). Similar results were observed for patients achieving at least 50% or 75% repigmentation (i.e., 4 to 6 times higher odds of achieving at least 50% or 75% response with ruxolitinib 1.5% cream).

Table 5. Modelled estimates (OR): F-VASI/RPS ruxolitinib 1.5% cream vs NB-UVB + TCS combination therapy at 9 months (Week 40)

Repigmentation Response/ Outcome (F-VASI)	Naive Estimates (Unweighted)	MAIC Estimates (Weighted)
	Odds Ratio (SE) [95% CL; p-value] Rux 1.5% Cream vs NB-UVB + TCS	Odds Ratio (SE) [95% CL; p-value] Rux 1.5% Cream vs NB-UVB + TCS
0-24%	[redacted] **p<0.001]***	[redacted] **p<0.001]***
25-100%	[redacted] **p<0.001]***	[redacted] **p<0.001]***
50-100%	[redacted] **p<0.001]***	[redacted] **p<0.001]***
75-100%	[redacted] **p<0.001]***	[redacted] **p<0.001]***

Abbreviations: CL, confidence level; NB-UVB, narrowband ultraviolet B; Rux, ruxolitinib; SE, standard error; TCS, topical corticosteroid.
*Statistically Significant at the 2 sided 5% level
Effective Sample Size (ESS) for Ruxolitinib 1.5% Cream (vs NB-UVB) at week 40: 287

Comparison of ruxolitinib 1.5% cream and NB-UVB ± TCS at 6 months (24 weeks)

Figure 1 summarises the proportion of patients in each treatment response category (0-24% [non-responders]; 25-100%; 50-100%; 75-100%) following 6 months of treatment with ruxolitinib 1.5% cream, NB-UVB monotherapy or NB-UVB + TCS.

Ruxolitinib for treating non-segmental vitiligo in people 12 years and over [ID3998]

Draft guidance comments form

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Figure 1. Comparison of proportion of patients for each repigmentation response: MAIC Estimates (OR) for Ruxolitinib 1.5% Cream vs NB-UVB and NB-UVB ± TCS at 6 months (Week 24)

Abbreviations: CL, confidence level; NB-UVB, narrowband ultraviolet B; TCS, topical corticosteroid.

Strength of relationship between F-VASI and T-VASI

Treatment effects from T-VASI and F-VASI (computed separately) at 6 months and 9 months were plotted and showed good agreement with a moderate to strong correlation (Pearson correlation of 0.81; p<0.001) (**Figure 2**Error! Reference source not found.), hence, confirming treatment differences between ruxolitinib cream and NB-UVB observed from F-VASI and RPS are well aligned.

Figure 2. Correlation plot of differences in proportions of F-VASI and T-VASI for Ruxolitinib 1.5% Cream vs NB-UVB ± TCS across 6 months (24 weeks) and 9 months (40 weeks)

	 Abbreviations: F-VASI, facial vitiligo area scoring index; NB-UVB, narrowband ultraviolet B; TCS, topical corticosteroid; T-VASI, total vitiligo area scoring index. Conclusions: • Results from the MAIC analysis demonstrated that ruxolitinib 1.5% cream had statistically significantly improved repigmentation response rates compared to phototherapy (either as monotherapy or combination therapy with TCS) after 6 and 9 months of treatment, across multiple response categories (**Table 4**, **Table 5** and **Figure 1**). • On average, between 6 and 9 months of treatment, patients on ruxolitinib 1.5% cream were 3 to 8 times more likely to have repigmentation improvements compared with phototherapy (either as monotherapy or combination therapy) across all response categories. • Both naïve (unweighted) and population-adjusted (weighted) estimates were consistent in demonstrating improved repigmentation responses for patients on ruxolitinib 1.5% cream compared with phototherapy (either as monotherapy or combination therapy). • There was a moderate to strong correlation between treatment effects from T-VASI and F-VASI (Pearson correlation of 0.81; p<0.001) (**Figure 2**Error! Reference source not found.).
5	**Ruxolitinib 1.5% cream in prior therapy subgroups (response to committee comments in ACD Section 3.6)** The committee requested that the company submit a full submission of evidence for participants in the TRuE-V studies who had received prior therapy for their NSV. As per the committee's request, the company has submitted all available evidence from the pooled TRuE-V studies pertaining to the efficacy of ruxolitinib 1.5% cream in the overall population, prior therapy population and prior TCS/topical calcineurin inhibitor (TCI) population. It is important to note that the TRuE-V studies do not allow for

differentiation between those treated with TCS or TCI; that is, the percentages of patients who were previously treated with TCS or TCI are not mutually exclusive. From the studies, 28.0% of participants had previously been treated with TCS, 31.8% with TCIs and 31.9% with NB-UVB therapy.

The prior therapy population from the pooled TRuE-V studies is representative of the target population for this appraisal and demonstrated a slightly higher response rate with ruxolitinib 1.5% cream compared with the overall trial population (**Table 6**).

Table 6. Proportion of patients achieving F-VASI75 response in the prior therapy subgroup and overall population of the pooled TRuE-V studies at 24 weeks

Responders, %	Prior therapy subgroup (n=408)			Overall population (n=661)		
	Ruxolitinib 1.5% cream	Vehicle cream	OR (p-value)	Ruxolitinib 1.5% cream	Vehicle cream	OR (p-value)
F-VASI75	32.9%	9.6%	**4.6 (p<0.0001)**	30.7%	9.6%	**4.17 (p<0.0001)**

Abbreviations: F-VASI, facial vitiligo area scoring index; OR, odds ratio

The committee also requested a comparison of ruxolitinib 1.5% cream to phototherapy in the prior treated population; however, this ITC was not feasible using available evidence from the HI-Light trial, which is the only identified study with relevant effectiveness data for phototherapy, as subgroup data were not presented for participants who received prior therapy.[1,2]

6

Revised dosing assumptions (response to committee comments in ACD Section 3.9)

The company accepts the committee's preference that the mean dose of ruxolitinib cream from the pooled TRuE-V studies should be used in the cost-effectiveness model, using appropriate methods to account for any missing data. The data from the pooled TRuE-V studies on ruxolitinib usage were limited by missing data for nine randomised patients (six patients treated with ruxolitinib 1.5% cream and three patients with vehicle cream) who discontinued study treatment and whose treatment duration was not recorded. For these nine patients, their duration of treatment was imputed as 1 day, with the total weight of drug applied assumed to be the same as their mean daily dose (which ranged between 117 g and 237 g). When calculating the average dosage of ruxolitinib cream, inclusion of these outliers results in higher mean estimates.

In response to the committee's request for the individual patient-level body surface area (BSA) and dosing data from the TRuE-V trials, the company submitted an evidence package to NICE on 19 February 2024 which included the requested data as well as real-world evidence on BSA and consumption of ruxolitinib 1.5% cream in patients with NSV.

	In addition, the company has updated their base case dosing assumption with an estimated mean daily dose of treatment, which was calculated by applying a lognormal distribution to the TRuE-V trial dosing data in its entirety. An alternative scenario is also presented in which the mean dose of treatment was calculated with the nine outliers excluded from the analysis. The two analyses are described further below. Estimating mean daily dose by applying a lognormal distribution The application of a lognormal distribution was the company's preferred approach for estimating the mean dose of ruxolitinib cream as the data in its entirety could be analysed with no loss of information, including the nine outliers. Using this method, the estimated mean daily dose of study drug for the log-transformed data was 3.84 g (exponentiated; normal scale) for ruxolitinib 1.5% cream and 3.73 g (exponentiated; normal scale) for vehicle cream. Estimating mean daily dose by excluding the nine patients with missing data When the exposure time data of the nine outlier patients from TRuE-V were excluded, the mean daily dose of study drug was estimated to be 4.53 g (SD: 4.301) for ruxolitinib 1.5% cream and 4.54 g (SD: 4.816) for vehicle cream. Comparison of estimated dosing from TRuE-V trial data and real-world evidence for ruxolitinib 1.5% cream consumption As summarised in **Table 7**, multiple sources reporting real-world evidence from patients with vitiligo across Europe and the US demonstrate that the average daily dose of ruxolitinib 1.5% cream in line with its product label is expected to be lower in clinical practice than what was observed in the pooled TRuE-V studies. Compared with an estimated mean daily dose of 3.84 g to 4.53 g (depending on the analysis method used), the mean daily dose of ruxolitinib cream in real-world practice was estimated to range from [redacted]. This suggests that the lower estimate for the mean dose of ruxolitinib from the TRuE-V trials (lognormal analysis) is more reflective of clinical practice and the most appropriate estimate for the base-case cost-effectiveness analysis. The difference in ruxolitinib cream usage observed in the trials versus real-world practice could be explained by the BSA restriction in the trial inclusion criteria which limited the trial population to patients with 3.5% to 10% BSA, resulting in a trial population with a higher mean BSA (7.4%) compared with those observed in real-world studies (1.4% to 3.8%). This is further supported by clinical expert feedback from a German-based clinician who is currently treating patients with ruxolitinib 1.5% cream for NSV. The clinical expert informed the company that patients choose to treat visible areas (including face, neck, arms, hands and knees) and not their full affected BSA, with a mean surface involvement of approximately 4%.[6] The clinical expert estimated that ruxolitinib cream consumption would range from 2 to 10 tubes per year, with a mean of approximately 5 to 6 tubes, which is substantially lower than the 14 to 17 tubes per year observed in the TRuE-V studies.

Table 7. Trial data and real-world evidence on depigmented area BSA of people with vitiligo and their usage of ruxolitinib 1.5% cream

Data source		Depigmented area BSA	Daily dose (grams/day)	Number of 100-gram tubes per year
Clinical trial	TRuE-V1 and TRuE-V2[†]	Median of 7.7%	Median of 4.03 g/day (observed)	14.7 (observed)
	TRuE-V1 and TRuE-V2[‡]	Mean of 7.4%	Mean log transformed of 3.84 g/day Mean of 4.53 g/day (observed; 9 outliers excluded)	14.0 (observed) 16.5 (observed)
Real-world evidence	VALIANT (Europe)[3]	Median of 3.78%	2.23 g/day (estimated)*	8 (estimated)
	University Hospital Ghent (Belgium)[4]	Median of 2.0%	1.18 g/day (estimated)*	4.3 (estimated)
	VIOLIN (France)[5]	Median of 1.4%	0.83 g/day (estimated)*	3 (estimated)
	Opzelura® (ruxolitinib 1.5% cream) US data consumption (1 year)[§]	Not recorded	[redacted] (observed)	[redacted] (observed)
	Opzelura® (ruxolitinib 1.5% cream) US data renewal data (1 year)[¶]	Not recorded	Not recorded	[redacted] (observed)

Abbreviations: BSA, body surface area; US, United States.
[†]TRuE-V pooled median weight of study drug applied daily during the double-blind period for total (ruxolitinib cream and vehicle cream) population
[‡]Using the update dosage analysis data
[§]1-year US data on ruxolitinib 1.5% cream dispensed to vitiligo patients during the first 12 months (IQVIA LAAD data)
[¶]1-year US data on ruxolitinib 1.5% cream dispensed to vitiligo patients during the first 12 months (IQVIA treatment (TRx) and renewals (NRx) data; for every new prescription, there are 2.22 renewals)
*Calculations are based on observed ruxolitinib 1.5% cream consumption per BSA recorded in TRuE-V1 and TRuE-V2 at 24 weeks (0.59 g/BSA/day).

Impact of dosing assumptions on cost-effectiveness analyses

The impact of the dosing assumption for ruxolitinib cream on the updated cost-effectiveness analysis are presented in **Table 8**. The company has accepted the

mean daily dose from the pooled TRuE-V trials as their updated base case, which was calculated by applying a lognormal distribution to all dosing data, including the outliers. In the company's original base-case, the daily dose of ruxolitinib cream was assumed to be 4.03 g, which lies between the new mean estimates of 3.84 g (lognormal analysis) and 4.54 g (outliers excluded). The use of the mean daily dose from the TRuE-V studies is a conservative assumption considering clinical expert opinion and several real-world evidence studies suggest that the mean daily use of ruxolitinib 1.5% cream in practice is likely to be considerably lower than those observed in the TRuE-V studies. When the estimated mean daily dose of ruxolitinib 1.5% cream is based on the real-world VALIANT study (2.23 g/day),[3] the ICER decreases by 42% from the base case.

Table 8. Scenario analyses for dosing assumptions for ruxolitinib 1.5% cream

Method	Average daily dose of ruxolitinib cream	ICER vs no active treatment followed by NB-UVB	Change from base case
Applying lognormal distribution to TRuE-V data (base case)	**Mean of 3.84 g**	**£18,103**	**NA**
Observed TRuE-V data (company's original base case)	Median of 4.03 g	£19,011	+908
TruE-V data excluding 9 patients with outliers	Mean of 4.53 g	£21,400	+3,297
Estimated mean from VALIANT*[3]	Mean of 2.23 g	£10,411	-7,692

Abbreviations: ICER, incremental cost-effectiveness ratio; NA, not applicable; NB-UVB, narrowband ultraviolet B.
*Observed BSA data from VALIANT were used to calculate the mean dose based on observed ruxolitinib 1.5% cream consumption per BSA recorded in TRuE-V1 and TRuE-V2 at 24 weeks (0.59 g/BSA/day).

7

Revised costs and resource use assumptions (response to committee comments in ACD Sections 3.10 and 3.11)

The company acknowledges the committee's concerns related to the use of phototherapy in the non-response state. In the updated cost-effectiveness analyses, modelled patients do not receive NB-UVB in the non-response health state for the comparison of ruxolitinib 1.5% cream vs NB-UVB (either as monotherapy or in combination with TCS) or no active treatment only. For the comparison of ruxolitinib 1.5% cream with no active treatment followed by phototherapy, 25% of patients are assumed to receive NB-UVB in the non-response health state, in line with the opinion of the clinical advisors to the committee.

In addition, a cost of £0 is applied to no active treatment (previously referred to in the model as vehicle cream).

Further, the company has revised their disease management resource use assumptions, including psychological support, in line with the committee preference of assuming 15% of patients receive psychological support across all health states

and dermatology consultations. **Table 9** presents a summary of the model revisions relating to resource use.

Table 9. Summary of updates in healthcare resource utilisation parameters

Resource Use	Original Submission	Updated value
Initial, maintenance periods and retreated		
Dermatologist outpatient consultation	0.41	0.41
Dermatologist telephone appointment	0.00	0.00
Dermatologist nurse visit	0.04	0.04
GP consultation	0.01	0.01
A&E visit	0.03	0.03
Psychological support	0.69	0.15
Stable disease and stable retreated states		
Dermatologist outpatient consultation	0.19	0.19
Dermatologist telephone appointment	0.19	0.19
Dermatologist nurse visit	0.08	0.08
GP consultation	0.00	0.00
A&E visit	0.00	0.00
Psychological support	0.23	0.15
Non-response state		
Dermatologist outpatient consultation	0.42	0.15
Dermatologist telephone appointment	0.01	0.00
Dermatologist nurse visit	0.29	0.00
GP consultation	0.01	0.01
A&E visit	0.01	0.01
Psychological support	1.38	0.15

Abbreviations: A&E, Accident and Emergency; GP, general practitioner.

8

Utility values (response to committee comments in ACD Section 3.12)

The company is pleased that the committee agreed with the approach to utility estimation and acknowledged its plausibility. Further, as described in Comment 2, the company has updated the definition of response from F-VASI75 to F-VASI25, in line with committee preference and the SmPC for ruxolitinib 1.5% cream.[7] This means that weighting of utility in the non-response health state is not required as patients with F-VASI50 are no longer defined as non-responders in the model.

9

Costs and utility implications of adverse events (response to committee comments in ACD Section 3.13)

The committee concluded that the company should incorporate utility and cost implications of adverse events occurring in at least 1% of the population in any treatment group, including NB-UVB.

However, the company disagrees with this approach as the majority of adverse events experienced by patients in the TRuE-V trial treated with ruxolitinib 1.5% cream were mild and transient, and therefore not expected to affect patients' HRQoL

or lead to additional costs to the NHS that would materially impact on the cost-effectiveness results. Further detail can be found in Appendix A.

In addition, the inclusion of costs and utility implications of adverse events in the model would likely favour ruxolitinib 1.5% cream. **Table 10** provides the rates of adverse events included in the model. Erythema was reported in a substantially higher proportion of patients treated with NB-UVB in the HI-Light study (17%) compared with patients treated with ruxolitinib 1.5% cream in the pooled TRuE-V studies (2%). In addition, skin exfoliation and skin thinning were exclusively reported in patients treated with NB-UVB in the HI-Light study (3% and 1%, respectively), with no cases reported in patients in the pooled TRuE-V studies. Although ruxolitinib 1.5% cream was associated with a higher prevalence of nasopharyngitis (4%), headache (6%) and upper respiratory tract infection (3%) than NB-UVB (0% for all), this is likely to be associated with the fact the TRuE-V studies were conducted during the COVID-19 pandemic. Therefore, when considering adverse events which could impact costs and utilities in real-world practice (i.e., erythema, skin exfoliation and skin thinning), any disutilities from adverse events are likely to be of a greater magnitude with NB-UVB than with ruxolitinib 1.5% cream.

Table 10. Rates of adverse events included in the economic model for participants treated with ruxolitinib 1.5% cream or no active treatment in pooled TRuE-V studies (24 weeks) and NB-UVB in HI-Light (40 weeks)

Adverse event	Ruxolitinib 1.5% cream, %	No active treatment, %	NB-UVB, %
Acne (incl. application site)	6.24	1.34	0.59
Pruritus (incl. application site)	6.46	3.57	5.33
Nasopharyngitis	4.45	2.23	0.00
Headache	5.57	2.68	0.00
Upper respiratory tract infection	3.34	2.23	0.00
Erythema (incl. application site)	1.56	0.45	17.16
Skin exfoliation	0.00	0.00	2.96
Skin thinning	0.00	0.00	1.18

Ruxolitinib for treating non-segmental vitiligo in people 12 years and over [ID3998]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 21 February 2024. Please submit via NICE Docs.

10	**The cost-effectiveness threshold should consider that ruxolitinib cream is an innovative treatment for NSV (response to committee comments in ACD Section 3.16)** The company is disappointed that the committee did not identify additional benefits of ruxolitinib cream not captured in the economic modelling and concluded that all additional benefits of ruxolitinib cream had already been considered. Ruxolitinib 1.5% cream is an innovative topical formulation containing a small molecule JAK1/2 inhibitor which directly targets vitiligo pathogenesis with a mechanism of action that is different to other treatments used in the NHS for NSV. Moreover, ruxolitinib 1.5% cream has been proven as an effective treatment for a previously overlooked disease area that currently has no licensed treatment options. As such, the similarities between the innovative nature of ruxolitinib cream in NSV and ritlecitinib in alopecia areata are notable and the company strongly believe that ruxolitinib 1.5% cream should be subject to appraisal against a threshold consistent with the recent appraisal of ritlecitinib (ID4007). When considering the cost-effectiveness estimates for ruxolitinib 1.5% cream, it is also crucial to note that EQ-5D may not fully capture the health-related quality of life impairment of patients living with vitiligo. In the HI-Light study[1], a ceiling effect was observed in the EQ-5D data, whereby many patients at baseline reported almost "perfect health" (mean EQ-5D-5L utility score at baseline of 0.90) on the EQ-5D instrument and therefore were unable to report an improvement from baseline in a responder analysis. This may be attributed to the long mean duration of vitiligo among patients enrolled in the HI-Light study (11 years) and in the TRuE-V studies (14.8 years) that could have led to patients' adaptation to this chronic condition. The EQ-5D utility estimates derived from the TRuE-V studies, are likely to be affected in the same manner.

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading

them. You can resubmit your comments form without attachments, it must send it by the deadline.

- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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

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

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ruxolitinib for treating non-segmental vitiligo in people 12 years and over [ID3998]

Appendix A: Updated cost-effectiveness analysis

March 2024

File name	Version	Contains confidential information	Date
ID3998 Appendix A Updated ruxolitinib 1.5% cream cost effectiveness model_REDACTED	Version 1	No	28 March 2024

Table of Contents

List of Tables

List of Figures

Abbreviations

ACD	Appraisal consultation document
AE	Adverse event
BSA	Body surfance area
BSC	Best supportive care
CEAC	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CI	Confidence interval
CL	Confidence levels
COVID-19	Coronavirus Disease 2019
EAG	External assessment group
ESS	Effective sample size
EXP	Exponential
F-VASI	Facial vitiligo area scoring index
GEE	Generalised estimating equations
GP	General practitioner
Hi-Light	Home intervention of light therapy
HRQoL	Health related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ITC	Indirect treatment comparison
ITT	Intent-to-treat
LN	Natural logarithm
LTE	Long-term extension
MAIC	Matching adjusted indirect comparison
NB-UVB	Narrow-band ultraviolet B
NHS	National health service
NHSE	National health service England
NICE	National Institute for Health and Care Excellence
NMB	Net monetary benefit
OR	Odds ratio
OWSA	One way sensitivity analysis

PAS	Patient access scheme
PSA	Probabilistic sensitivity analysis
PSSRU	Personal social services research unit
QALY	Quality adjusted life years
RCT	Randomised clinical trial
RPS	Repigmentation scores
SD	Standard deviation
SE	Standard error
SmPC	Summary of product characteristics
TCI	Topical calcineurin inhibitor
TCS	Topical corticosteroid
TEAE	Treatment emergent adverse event
TRuE-V	Topical ruxolitinib evaluation in vitiligo
T-VASI	Total body vitiligo area scoring index
UK	United Kingdom
VALIANT	The Vitiligo and Life Impact Among International Communities study
VNS	Vitiligo noticeability scale
WAVG	Weighted average
WTP	Willingness to pay

This additional data submission presents the results of an indirect treatment comparison (ITC) between ruxolitinib cream and narrow-band ultraviolet B (NB-UVB), as well as the updates to the cost-effectiveness model made by the Company following publication of the draft guidance in order to address comments in the ACD, align with the committee preferences, and ensure the presented evidence is aligned with the NHS clinical practice and intended use of ruxolitinib 1.5% cream in the care pathway.

1 Indirect treatment comparison

An indirect treatment comparison (naïve) and a matching-adjusted indirect comparison (MAIC) were conducted to assess the clinical effectiveness of ruxolitinib 1.5% cream versus NB-UVB, and NB-UVB in combination with potent topical corticosteroid (TCS), in patients with non-segmental vitiligo following a specific request from NICE.

1.1 Data sources

Published aggregate data on the efficacy of NB-UVB from the HI-Light trial was used to derive an indirect treatment comparison between ruxolitinib 1.5% cream and phototherapy, either as monotherapy (NB-UVB) or combination therapy (NB-UVB & TCS). The objective of the HI-Light trial was to determine the effectiveness of (i) handheld narrowband UVB (NB-UVB) and (ii) a combination of potent topical corticosteroid (TCS) consisting of mometasone furoate 0·1% ointment and NB-UVB, compared with TCS alone, for localized vitiligo. The trial was designed as a randomised (1:1:1) pragmatic three-arm (NB-UVB; NB-UVB+TCS and TCS alone), placebo-controlled trial where patients were treated for 9 months with a 12-month follow-up. Participants were recruited from secondary care and the community, aged ≥ 5 years and with active vitiligo affecting < 10% of skin. TCS was applied once daily on alternating weeks; NB-UVB was administered on alternate days in escalating doses, adjusted for erythema. The primary outcome was treatment success at 9 months at a target patch assessed using the participant-reported Vitiligo Noticeability Scale (VNS). Secondary outcomes included percentage repigmentation at the target patch at 3, 6 and 9 months, using blinded clinician assessment of digital images (0–24%, 25–49%, 50–74%, 75–100%)[1].

Outcome data for ruxolitinib 1.5% cream was derived from the pooled TRuE-V studies[2]. The primary outcome measure of Facial Vitiligo Area Scoring Index (F-VASI) was used to inform the treatment comparison. Outcome data for monotherapy (NB-UVB) and combination therapy (NB-UVB & TCS) was derived from published results from the HI-Light trial[3].

1.2 Methodology

A naïve (unweighted) and a matching-adjusted (weighted) indirect comparison (MAIC) was conducted in the overall population to compare ruxolitinib 1.5% cream and phototherapy (either as monotherapy or combination therapy) after 6 and 9 months of treatment (24 and 40 weeks from TRuE-V, respectively, were chosen as these were the timepoints of response assessment that more closely reflected the assessment timepoints in HI-Light). The analysis was conducted in the overall population only, as data on previous treatment is not available in HI-Light and it was considered more appropriate to utilise the overall population from the TRuE-V studies and therefore obtain more precise estimates from the indirect treatment comparison.

The indirect treatment comparison requires the assumption that repigmentation scores (RPS) reported in the HI-Light trial are reasonably equivalent to F-VASI from TRuE-V. This assumption is supported by the notable similarities between how RPS and F-VASI are measured[4]. Specifically, a standard approach was used to measure total affected area in both HI-Light and the TRuE-V studies; the sum of lesions was expressed as a fraction of the total body surface area (BSA). The resulting change from baseline in total BSA informs RPS categorisation. The categorisation of repigmentation scores in HI-Light is consistent with that of F-VASI in the TRuE-V studies. In the HI-Light trial, repigmentation was classified in a similar manner to the TRuE-V trials. Hence, for the MAIC analyses, the following response categories were used as outcomes, and each outcome was analysed separately: (0%–24% (less than 25% repigmentation), 25%–100% (at least 25% repigmentation), 50%–100% (at least 50% repigmentation), and 75%–100% (at least 75% repigmentation)).

The naïve (unweighted) and weighted MAIC analyses included only patients who had a reported percentage change score recorded at follow-up at each of 6-month (24

week) and 9-month (40 week) timepoints from both the HI-Light and TRuE-V studies. The 6-month data from HI-Light aligned with the double-blind period of the TRuE-V studies and was used for comparability, and 9-month TRuE-V data aligned with a standard treatment course of NB-UVB. Participants who had been randomised to vehicle cream in the TRuE-V studies and crossed over to ruxolitinib 1.5% cream at week 24 were not included in the 9-month (week 40) analysis. Note that 'vehicle cream' is now referred to as 'no active treatment' and no costs have been attributed to it, in line with the committee's preference.

The MAIC involved a process of estimating optimal (propensity) weights for the 3 identified effect modifiers, which were selected based on clinical input among the mutually reported baseline characteristics between the TruE-V and HI-Light studies: age, sex and skin type (Fitzpatrick Skin Type: I-III) using SAS®. The method followed was that of Signorovitch et al., 2012 where optimal weights were generated through a non-linear optimization process using a Newton Raphson approach. This ensured a (sub) set of patients were matched from TRuE-V studies to the HI-Light study in terms of age, sex and skin type. Consequently, a comparison between ruxolitinib 1.5% cream and phototherapy (either as monotherapy or combination therapy) after adjusting for these weights takes into account imbalances in effect modifiers. A generalised estimating equations (GEE) approach was used in a frequentist framework (using PROC GENMOD in SAS®). The effective sample size (computed as a function of weights) was derived; relative effects were estimated and reported along with 95% confidence levels and p-values using estimated proportions and odds ratios (OR) (using a logit link function). This method is advocated by Signorovitch et al., 2012[5].

1.3 Results

1.3.1. Ruxolitinib 1.5% Cream vs NB-UVB (Monotherapy)

Matching criteria

Table 1 presents the pre- and post-matching variables and demonstrates successful matching of TRuE-V Participants to the HI-Light trial in the MAIC analysis.

Table 1. Baseline characteristics in the pooled TRuE-V studies before and after matching (Ruxolitinib 1.5% Cream vs NB-UVB)

Baseline Characteristic	Before Matching TRuE-V Pooled (Ruxolitinib 1.5% cream arm)	HI-Light (NB-UVB arm)	After Matching TRuE-V Pooled (Ruxolitinib 1.5% cream arm)
Mean Age (SD) (Years)	39.5 (15.4)	36.9 (18.9)	36.9 (14.8)
Sex (Male) %	45%	52%	52%
Fitzpatrick Skin Type (Type: I-III) %	72%	59%	59%

SD: Standard Deviation.

Odds Ratios: comparisons of Ruxolitinib 1.5% cream vs NB-UVB (Monotherapy) at 6-month (week 24) and 9-month (week 40)

Table 2 and **Table 3** present the odds ratios (OR) for the comparison between ruxolitinib 1.5% cream and NB-UVB at 6 and 9 Month (Week 24 and Week 40), respectively.

Table 2. Modelled Estimates (OR): F-VASI/RPS Ruxolitinib 1.5% Cream vs NB-UVB (Monotherapy) 6-month (Week 24)

	Naive Estimates (Unweighted)	MAIC Estimates (Weighted)
Repigmentation Response/Outcome (F-VASI)	Odds Ratio (SE) [95% CL; P-value] Rux 1.5% Cream vs NB-UVB	Odds Ratio (SE) [95% CL; P-value] Rux 1.5% Cream vs NB-UVB
0-24%	[redacted] **; p<0.001]***	[redacted] **; p<0.001]***
25-100%	[redacted] **; p<0.001]***	[redacted] **; p<0.001]***
50-100%	[redacted] **; p<0.001]***	[redacted] **; p<0.001]***
75-100%	[redacted] **; p<0.001]***	[redacted] **; p<0.001]***

Abbreviations: CL, Confidence Levels; F-VASI, facial vitiligo area scoring index; MAIC, matching-adjusted indirect comparison; RPS, repigmentation score; SE, Standard Error.
*Statistically Significant at the 2 sided 5% level.
Effective Sample Size (ESS) for Ruxolitinib 1.5% Cream (vs NB-UVB) at week 24: 384.

Table 3. Modelled Estimates (OR): F-VASI/RPS Ruxolitinib 1.5% Cream vs NB-UVB (Monotherapy) 9-month (Week 40)

	Naive Estimates (Unweighted)	**MAIC Estimates (Weighted)**
Repigmentation Response/Outcome (F-VASI)	Odds Ratio (SE) [95% CL; P-value] Rux 1.5% Cream vs NB-UVB	Odds Ratio (SE) [95% CL; P-value] Rux 1.5% Cream vs NB-UVB
0-24%	[redacted]; **p<0.001]***	[redacted]; **p<0.001]***
25-100%	[redacted]; **p<0.001]***	[redacted]; **p<0.001]***
50-100%	[redacted]; **p<0.001]***	[redacted]; **p<0.001]***
75-100%	[redacted]; **p<0.001]***	[redacted]; **p<0.001]***

Abbreviations: CL, Confidence Levels; F-VASI, facial vitiligo area scoring index; MAIC, matching-adjusted indirect comparison; RPS, repigmentation score; SE, Standard Error.
*Statistically Significant at the 2 sided 5% level.
Effective Sample Size (ESS) for Ruxolitinib 1.5% Cream (vs NB-UVB) at week 40: 326

MAIC results show, by 24 weeks (6 months), ruxolitinib 1.5% cream being more than 3 times likely to confer at least 25% improvement in repigmentation compared to NB-UVB: (OR= [redacted], p<0.001); after 40 weeks (9 months) this improvement was almost 8 times more likely with ruxolitinib 1.5% cream compared to NB-UVB: OR= [redacted], p<0.001).

Similar results were observed for patients achieving at least 50% or 75% improvement in repigmentation. Patients on ruxolitinib 1.5% cream were around 6 to 7 times more likely to achieve at least 50% repigmentation after 6 months of treatment and around 7 to 8 times more likely to achieve at least 50% repigmentation after 9 months of treatment compared to NB-UVB. The naïve estimates showed similar conclusions.

Difference in Proportions: comparisons of Ruxolitinib 1.5% cream vs NB-UVB (Monotherapy) at 6-month (week 24) and 9-month (week 40)

Comparisons in terms of absolute differences in proportions showed similar conclusions (**Table 4** and **Table *5***) to OR estimates for ruxolitinib 1.5% cream vs NB-UVB. A higher proportion of patients achieved at least 25% re-pigmentation on ruxolitinib 1.5% cream vs NB-UVB at 24 weeks ([redacted]; p<0.001) and at 40 weeks ([redacted]; p<0.001).

Differences of 37% ([redacted]; p<0.001) for ruxolitinib 1.5% cream vs NB-UVB at week 24 and 44% ([redacted] p<0.001) for ruxolitinib 1.5% cream vs NB-UVB at week 40 were observed for patients classed as achieving at least a 50% improvement in repigmentation. Modelled proportion estimates at 9 months (i.e., 40 weeks) are used in the cost-effectiveness analysis (2.1).

Table 4. Modelled Estimates (Proportions): F-VASI/RPS Ruxolitinib 1.5% Cream vs NB-UVB (Monotherapy) 6-month (Week 24)

		Naive Estimates (Unweighted)			MAIC Estimates (Weighted)		
Repigmentation Response/Outcome (F-VASI)		**NB-UVB**	**Ruxolitinib 1.5% Cream**	**Difference (SE) [95% CL; P-value] Rux 1.5% Cream vs NB-UVB**	**NB-UVB**	**Ruxolitinib 1.5% Cream**	**Difference (SE) [95% CL; P-value] Rux 1.5% Cream vs NB-UVB**
0-24%	Estimate (SE)	[redacted]	[redacted]	[redacted];	[redacted]	[redacted]	[redacted]
	95% CL	[redacted]	[redacted]	**p<0.001]***	[redacted]	[redacted]	**p<0.001]***
25-100%	Estimate (SE)	[redacted]	[redacted]	[redacted];	[redacted]	[redacted]	[redacted];
	95% CL	[redacted]	[redacted]	**p<0.001]***	[redacted]	[redacted]	**p<0.001]***
50-100%	Estimate (SE)	[redacted]	[redacted]	[redacted];	[redacted]	[redacted]	[redacted];
	95% CL	[redacted]	[redacted]	**p<0.001]***	[redacted]	[redacted]	**p<0.001]***
75-100%	Estimate (SE)	[redacted]	[redacted]	[redacted];	[redacted]	[redacted]	[redacted];
	95% CL	[redacted]	[redacted]	**p<0.001]***	[redacted]	[redacted]	**p<0.001]***

Abbreviations: CL, Confidence Levels; F-VASI, facial vitiligo area scoring index; MAIC, matching-adjusted indirect comparison; RPS, repigmentation score; SE, Standard Error.
*Statistically Significant at the 2 sided 5% level.
Effective Sample Size (ESS) for Ruxolitinib 1.5% Cream (vs NB-UVB) at week 24: 384.

Table 5. Modelled Estimates (Proportions): F-VASI/RPS Ruxolitinib 1.5% Cream vs NB-UVB (Monotherapy) 9-month (Week 40)

		Naive Estimates (Unweighted)			MAIC Estimates (Weighted)		
Repigmentation Response/Outcome (F-VASI)		**NB-UVB**	**Ruxolitinib 1.5% Cream**	**Difference (SE) [95% CL; P-value] Rux 1.5% Cream vs NB-UVB**	**NB-UVB**	**Ruxolitinib 1.5% Cream**	**Difference (SE) [95% CL; P-value] Rux 1.5% Cream vs NB-UVB**
0-24%	Estimate (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CL	[redacted]	[redacted]	**p<0.001]***	[redacted]	[redacted]	**p<0.001]***
25-100%	Estimate (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CL	[redacted]	[redacted]	**p<0.001]***	[redacted]	[redacted]	**p<0.001]***
25-49%	Estimate (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50-100%	Estimate (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CL	[redacted]	[redacted]	**p<0.001]***	[redacted]	[redacted]	**p<0.001]***
50-74%	Estimate (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
75-100%	Estimate (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CL	[redacted]	[redacted]	**p<0.001]***	[redacted]	[redacted]	**p<0.001]***

Abbreviations: CL, Confidence Levels; F-VASI, facial vitiligo area scoring index; MAIC, matching-adjusted indirect comparison; RPS, repigmentation score; SE, Standard Error.
*Statistically Significant at the 2 sided 5% level.
Effective Sample Size (ESS) for Ruxolitinib 1.5% Cream (vs NB-UVB) at week 40: 326.

Figure 1. Modelled Estimates (Odds Ratio): F-VASI/RPS Ruxolitinib 1.5% Cream vs NB-UVB (Monotherapy): Week 24 & Week 40 Results

Abbreviations: CL, Confidence Levels; F-VASI, facial vitiligo area scoring index; MAIC, matching-adjusted indirect comparison; RPS, repigmentation score; SE, Standard Error.
Effective Sample Size (ESS) for Ruxolitinib 1.5% Cream (vs NB-UVB) at week 24: 384
Effective Sample Size (ESS) for Ruxolitinib 1.5% Cream (vs NB-UVB) at week 40: 326

1.3.2 Ruxolitinib 1.5% Cream vs NB-UVB & TCS (Combination Therapy)

Matching criteria

Table 6 presents the pre- and post-matching variables and demonstrates successful matching of TRuE-V Participants to the HI-Light trial in the MAIC analysis.

Table 6. Baseline characteristics in the pooled TRuE-V studies before and after matching (Ruxolitinib 1.5% Cream vs NB-UVB & TCS)

Baseline Characteristic	Before Matching TRuE-V Pooled (Ruxolitinib 1.5% cream arm)	HI-Light (Combination Therapy arm: NB-UVB & TCS)	After Matching TRuE-V Pooled (Ruxolitinib 1.5% cream arm)
Mean Age (SD) (Years)	39.5 (15.4)	37.0 (19.1)	37.0 (14.3)
Sex (Male) %	45%	60%	60%
Fitzpatrick Skin Type (Type: I-III) %	72%	54%	54%

Abbreviations: MAIC, matching adjusted indirect comparison; SD, standard deviation; TCS, topical corticosteroid.

Odds Ratios: comparisons of Ruxolitinib 1.5% cream vs NB-UVB & TCS (Combination Therapy) at 6-month (week 24) and 9-month (week 40).

Table 7 and

Table *8* present the OR for the comparison between ruxolitinib 1.5% cream and combination therapy (NB-UVB & TCS) at 6 and 9 Month (Week 24 and Week 40), respectively.

Table 7. Modelled Estimates (OR): F-VASI/RPS Ruxolitinib 1.5% Cream vs NB-UVB & TCS (Combination Therapy) 6-month (Week 24)

	Naive Estimates (Unweighted)	**MAIC Estimates (Weighted)**
Repigmentation Response/Outcome (F-VASI)	Odds Ratio (SE) [95% CL; P-value] Rux 1.5% Cream vs Combination Therapy	Odds Ratio (SE) [95% CL; P-value] Rux 1.5% Cream vs Combination Therapy
0-24%	[redacted]; p<0.001]*	[redacted]; p<0.001]*
25-100%	[redacted]; p<0.001]*	[redacted]; p<0.001]*
50-100%	[redacted]; p<0.001]*	[redacted]; p<0.001]*
75-100%	[redacted]; p<0.001]*	[redacted]; p<0.001]*

Abbreviations: CL, Confidence Levels; F-VASI, facial vitiligo area scoring index; MAIC, matching-adjusted indirect comparison; RPS, repigmentation score; SE, Standard Error.
*Statistically Significant at the 2 sided 5% level.
Effective Sample Size (ESS) for Ruxolitinib 1.5% Cream (vs Combination Therapy) at week 24: 338.

Table 8. Modelled Estimates (OR): F-VASI/RPS Ruxolitinib 1.5% Cream vs NB-UVB & TCS (Combination Therapy) 9-month (Week 40)

	Naive Estimates (Unweighted)	**MAIC Estimates (Weighted)**
Repigmentation Response/Outcome (F-VASI)	Odds Ratio (SE) [95% CL; P-value] Rux 1.5% Cream vs Combination Therapy	Odds Ratio (SE) [95% CL; P-value] Rux 1.5% Cream vs Combination Therapy
0-24%	[redacted]; p<0.001]*	[redacted]; p<0.001]*
25-100%	[redacted]; p<0.001]*	[redacted]; p<0.001]*
50-100%	[redacted]; p<0.001]*	[redacted]; p<0.001]*
75-100%	[redacted]; p<0.001]*	[redacted]; p<0.001]*

Abbreviations: SE: Standard Error; CL: Confidence Levels.
*Statistically Significant at the 2 sided 5% level.
Effective Sample Size (ESS) for Ruxolitinib 1.5% Cream (vs Combination Therapy) at week 40: 287.

MAIC results show, by 24 weeks, ruxolitinib 1.5% cream being around three times more likely to confer at least 25% improvement in repigmentation compared to combination therapy: (OR= [redacted], p<0.001); after 40 weeks, improvement of repigmentation was almost 6 times more likely with ruxolitinib 1.5% cream compared to combination therapy: OR= [redacted] ([redacted], p<0.001).

Similar results were also observed for patients achieving at least 50% or 75% improvement in repigmentation: patients on ruxolitinib 1.5% cream were around 3 times more likely to achieve at least 50% repigmentation after 6 months of treatment

and around 4 to 6 times more likely to achieve at least 50% repigmentation after 9 months of treatment compared to combination therapy. The naïve estimates showed similar conclusions.

Difference in Proportions: comparisons of Ruxolitinib 1.5% cream vs NB-UVB & TCS (Combination Therapy) at 6-month (week 24) and 9-month (week 40)

Comparisons in terms of absolute differences in proportions showed similar conclusions (**Table 9** and **Table 10**) to OR estimates for ruxolitinib 1.5% cream vs NB-UVB & TCS. A higher proportion of patients achieved at least 25% re-pigmentation on ruxolitinib 1.5% cream vs combination therapy at 24 weeks ([redacted]; p<0.001) and at 40 weeks ([redacted]; p<0.001). Differences of 25% ([redacted]; p<0.001) for ruxolitinib 1.5% cream vs combination therapy at week 24 and 40% ([redacted]; p<0.001) for ruxolitinib 1.5% cream vs combination therapy at week 40 were observed for patients classed as achieving at least a 50% improvement in repigmentation.

Table 9. Modelled Estimates (Proportions): F-VASI/RPS Ruxolitinib 1.5% Cream vs NB-UVB & TCS (Combination Therapy) 6-month (Week 24)

		Naive Estimates (Unweighted)			MAIC Estimates (Weighted)		
Repigmentation Response/Outcome (F-VASI)		**Combination (NB-UVB & TCS)**	**Ruxolitinib 1.5% Cream**	**Difference (SE) [95% CL; P-value] Rux 1.5% Cream vs Combination Therapy**	**Combination (NB-UVB & TCS)**	**Ruxolitinib 1.5% Cream**	**Difference (SE) [95% CL; P-value] Rux 1.5% Cream vs Combination Therapy**
0-24%	Estimate (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CL	[redacted]	[redacted]	**p<0.001]***	[redacted]	[redacted]	**p<0.001]***
25-100%	Estimate (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CL	[redacted]	[redacted]	**p<0.001]***	[redacted]	[redacted]	**p<0.001]***
50-100%	Estimate (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CL	[redacted]	[redacted]	**p<0.001]***	[redacted]	[redacted]	**p<0.001]***
75-100%	Estimate (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CL	[redacted]	[redacted]	**p<0.001]***	[redacted]	[redacted]	**p<0.001]***

Abbreviations: CL, Confidence Levels; F-VASI, facial vitiligo area scoring index; MAIC, matching-adjusted indirect comparison; RPS, repigmentation score; SE, Standard Error; TCS, topical corticosteroids.
*Statistically Significant at the 2 sided 5% level.
Effective Sample Size (ESS) for Ruxolitinib 1.5% Cream (vs Combination Therapy) at week 24: 338.

Table 10. Modelled Estimates (Proportions): F-VASI/RPS Ruxolitinib 1.5% Cream vs NB-UVB & TCS (Combination Therapy) 9-month (Week 40)

	Naive Estimates (Unweighted)			MAIC Estimates (Weighted)		
Repigmentation Response/Outcome (F-VASI)	**Combination (NB-UVB & TCS)**	**Ruxolitinib 1.5% Cream**	**Difference (SE) [95% CL; P-value]**	**Combination (NB-UVB & TCS)**	**Ruxolitinib 1.5% Cream**	**Difference (SE) [95% CL; P-value] Rux 1.5% Cream vs**

				Rux 1.5% Cream vs Combination Therapy			Combination Therapy
0-24%	Estimate (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CL	[redacted]	[redacted]	**p<0.001]***	[redacted]	[redacted]	**p<0.001]***
25-100%	Estimate (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CL	[redacted]	[redacted]	**p<0.001]***	[redacted]	[redacted]	**p<0.001]***
25-49%	Estimate (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CL	[redacted]	[redacted]	p=0.5589]	[redacted]	[redacted]	p=0.4971]
50-100%	Estimate (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CL	[redacted]	[redacted]	**p<0.001]***	[redacted]	[redacted]	**p<0.001]***
50-74%	Estimate (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CL	[redacted]	[redacted]	**p=0.0051]***	[redacted]	[redacted]	**p=0.0044]***
75-100%	Estimate (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CL	[redacted]	[redacted]	**p<0.001]***	[redacted]	[redacted]	**p<0.001]***

Abbreviations: CL, Confidence Levels; F-VASI, facial vitiligo area scoring index; MAIC, matching-adjusted indirect comparison; RPS, repigmentation score; SE, Standard Error; TCS, topical corticosteroids.
*Statistically Significant at the 2 sided 5% level
Effective Sample Size (ESS) for Ruxolitinib 1.5% Cream (vs Combination Therapy) at week 40: 287.

Figure 2. Modelled Estimates (Odds Ratio): F-VASI/RPS Ruxolitinib 1.5% Cream vs Combination Therapy (Week 24 & Week 40 Results)

Abbreviations: CL, Confidence Levels; F-VASI, facial vitiligo area scoring index; MAIC, matching-adjusted indirect comparison; RPS, repigmentation score; TCS, topical corticosteroids.
Effective Sample Size (ESS) for Ruxolitinib 1.5% Cream (vs Combination Therapy) at week 24: 338.
Effective Sample Size (ESS) for Ruxolitinib 1.5% Cream (vs Combination Therapy) at week 40: 287.

1.4 Conclusion

- MAIC analysis showed ruxolitinib 1.5% cream to have statistically improved repigmentation response rates compared to phototherapy, (either as monotherapy or combination therapy) after 6 and 9 months of treatment, across varying response categories.
- Comparisons in terms of absolute differences in proportions showed similar conclusions to odds ratios: ruxolitinib 1.5% cream showed better repigmentation performance than phototherapy (either as monotherapy or combination therapy), after 6 and 9 months of treatment, across varying response categories.
- On average, between 6 and 9 months of treatment, patients on ruxolitinib 1.5% cream were (approximately) between 3 to 8 times more likely to achieve improved repigmentation compared to phototherapy (either as monotherapy or combination therapy) across all response categories.
- Both naïve (unweighted) and population-adjusted (weighted) estimates were consistent in demonstrating improved repigmentation responses for patients on ruxolitinib 1.5% cream.
- Treatment effects from Total Body Vitiligo Area Scoring Index (T-VASI) and F-VASI (computed separately) at each of 6-months and 9-months were plotted and showed good agreement (**Figure *4***) with a moderate to strong correlation (Pearson correlation of 0.81; $p<0.001$), hence, confirming treatment differences between ruxolitinib cream and phototherapy observed from F-VASI and RPS are well aligned.

Figure 3. Comparison of proportion of patients for each repigmentation response: MAIC Estimates (OR) for Ruxolitinib 1.5% Cream vs Phototherapy (Monotherapy & Combination Therapy) at 6-month (Week 24)

Abbreviations: CL, Confidence Levels; MAIC, matching-adjusted indirect comparison; OR, odds ratio; TCS, topical corticosteroids.

Figure 4. Correlation plot of F-VASI and T-VASI Differences in proportions: Ruxolitinib 1.5% Cream vs Phototherapy (Monotherapy & Combination Therapy) across 6-months (24 Weeks) and 9-months (40 Weeks)

Abbreviations: F-VASI, facial vitiligo area scoring index; T-VASI, total body vitiligo area scoring index.

2 Cost-effectiveness analysis

2.1 Cost-effectiveness summary

The cost-effectiveness model was updated to a) align with the committee's preferences regarding the model structure and use of clinical data, as per the draft guidance, b) revise the model to reflect the desired positioning of ruxolitinib in the NHS England treatment pathway by incorporating a comparison against NB-UVB monotherapy and in combination with TCS, and c) to reflect the NHS clinical practice and the pooled TRuE-V Phase III studies[1] and TRuE-V long-term extension (LTE)[2] data and design more closely.

The cost-effectiveness analysis retains the same perspective, time horizon, discount rates and cost categories. However, health state utility values have been updated to align with the new definitions of response (described in Section 2.9). In the absence of HRQoL data from HI-Light specific to the response definitions used in the model, the utility analysis was updated to estimate response-based treatment-agnostic

utilities. The incremental cost-effectiveness ratio (ICER) of ruxolitinib cream versus either no active treatment or NB-UVB (including a simplified comparison vs NB-UVB+TCS) is evaluated in terms of the incremental cost per quality-adjusted life-year (QALY) gained. For the simplified comparison of ruxolitinib cream versus NB-UVB+TCS, the initial response in the model was informed by the F-VASI/RPS efficacy data from the combination arm in HI-Light study and the relevant MAIC-adjusted ruxolitinib cream data (see **Table 10**), while all the other model inputs remained the same with the comparison of ruxolitinib cream versus NB-UVB monotherapy.

Unless otherwise stated, all remaining features of the model remain unchanged.

2.2 Cost-effectiveness model comparisons and population

The updated cost-effectiveness analysis allows four comparisons:

- Ruxolitinib 1.5% cream versus no active treatment followed by NB-UVB (as per original submission)
- Ruxolitinib 1.5% cream versus no active treatment only
- Ruxolitinib 1.5% cream versus NB-UVB monotherapy
- Ruxolitinib 1.5% cream versus NB-UVB+TCS, where F-VASI/RPS efficacy data from the combination arm in Hi-Light study and the relevant MAIC-adjusted ruxolitinib cream data (see **Table 10**) inform initial response in the model.

As described in the original submission, the HI-Light trial was a 9-month study testing the efficacy of home-based light therapy and topical steroid cream, used alone or in combination, for the treatment of vitiligo. Published results from the HI-Light trial are limited to the overall population of the trial, since results for subgroups were not published [3]. The intent-to-treat (ITT) population of the pooled TRuE-V1 and TRuE-V2[1] studies and the ITT population of the HI-Light trial were used for the indirect comparison between ruxolitinib 1.5% cream and NB-UVB, respectively, to obtain more precise relative effectiveness estimates from the ITC. For consistency, the direct comparison of ruxolitinib 1.5% cream with no active treatment is based on the ITT populations of the pooled TRuE-V1 and TRuE-V21 studies.

The efficacy data informing the cost-effectiveness analysis are based on the pooled TRuE-V studies[1], the TRuE-V LTE study[2] and the HI-Light trial[3].

The additional cost-effectiveness analyses of ruxolitinib 1.5% cream vs NB-UVB with or without TCS support the submitted positioning of ruxolitinib cream as a step change option after failure of the treatment with TCS or topical calcineurin inhibitors (TCI).

2.3 Data used in the cost-effectiveness model

Published read-outs from HI-Light pertain to assessment timepoints of 3, 6, and 9 months[4]. In the TRuE-V studies, assessments were conducted at weeks 24, 28, 34, 40, 46 and 52[1]. To align with the timepoints available from the HI-Light trial, week 40 was used as our base-case given the duration of initial period is now updated to 52 weeks to align with the SmPC for ruxolitinib 1.5% cream[5] (see Section 2.7.1), making extrapolation from week 40 efficacy less uncertain. A linear extrapolation (i.e., constant probability of response) was assumed between week 40 and week 52. Double-blind efficacy data for no active treatment is only available up to week 24, hence a linear extrapolation was assumed between week 24 and week 52. The following section describes the updates to the cost-effectiveness analysis.

2.4 Updated cost-effectiveness analysis schematic and description

Significant changes were made to the model structure, assumptions and clinical data implementation to address the criticisms outlined in the draft recommendation as outlined in **Table 11**. The revised structure ensures better alignment of the modelled treatment sequence with the NHS clinical practice and the 2L positioning of ruxolitinib and reflects the trial data more accurately while accounting for the differences in study designs, treatment durations and paucity of data.

Table 11. Structural amendments to the economic model made in response to the Committee's suggestions

Committee comment in the draft guidance	Company response	Anticipated impact on ICER
Revise the model to enable comparisons with	Comparison with no active treatment followed by NB-UVB featured in the original model. A direct comparison with phototherapy (i.e., NB-UVB	NA

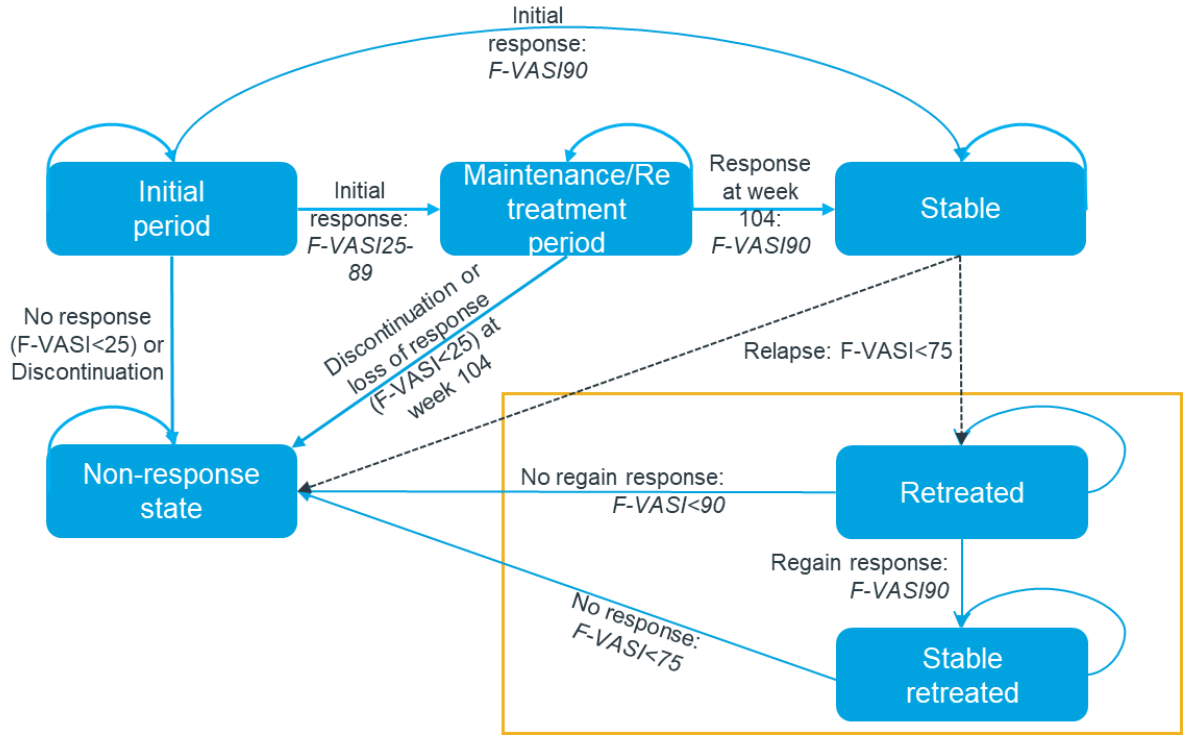
Committee comment in the draft guidance	Company response	Anticipated impact on ICER
• No active treatment, followed by NB-UVB (with or without topical treatments) • Phototherapy (with or without topical treatments)	either as monotherapy or in combinations with TCS) has been incorporated in the revised version	
Provide comparative efficacy of ruxolitinib vs phototherapy if ruxolitinib is positioned as 2L treatment	Company has conducted a MAIC to derive relative efficacy of ruxolitinib vs NB-UVB with or without topical treatments	NA
Economic model should be aligned with the ruxolitinib SmPC, trial data and clinical practice regarding response definitions, assessment timepoints and treatment duration	• Initial response is now defined as F-VASI25 at week 52 • Response is reassessed at week 104 to align with the duration of the TRuE-V & LTE studies and clinical practice	Large
Costs in non-response state should not be capped at 10 years	Costs in non-response state are now applied for lifetime	Moderate
Model should allow transition from the non-response state if there is an improvement of vitiligo on subsequent treatments	We could find no clinical data to inform transitions from the non-response to any states other than death. The possibility of retreatment was addressed through addition of optional retreated and stable retreated health states that patients can enter after a relapse	Unknown
For people reaching F-VASI75-89, model should allow transition from the maintenance to stable state	Transition has been implemented and is triggered by achievement of F-VASI90 at week 104	Moderate
Retreatment with vehicle cream does not reflect NHS clinical practice	Patients initiated on no active treatment* are retreated with ruxolitinib 1.5% cream	Low
Incorporate utility and cost for AEs occurring in ≥1% of people in any treatment group	No disutility data for AEs affecting skin	Unknown

Abbreviations: F-VASI, facial vitiligo area scoring index; F-VASI25-89, between 25% - 89% improvement from baseline; F-VASI25, 25% or greater improvement from baseline in F-VASI; F-VASI90, 90% or greater improvement from baseline in F-VASI; MAIC, matching adjusted indirect comparison; NHS, National Health Service; SmPC, summary of medicinal product characteristics; NB-UVB, narrow band ultraviolet B; TCS, topical corticosteroids; 2L, second line.

*In line with the removal of a cost for the vehicle cream, the Company have renamed it to 'no active treatment'.

While the model retains its seven state Markov design (**Figure 5**), the impact of these structural changes on health state occupancy and cohort movements are described below.

Figure 5. *Cost-effectiveness model schematic*



Abbreviations: F-VASI, facial vitiligo area scoring index.
Note: Dead, not presented in the figure for simplicity, is an absorbing state and can be reached from any of the other health states. In the maintenance/retreatment period, patients initiated on ruxolitinib 1.5% cream or no active treatment continue those treatments, while those initiated on NB-UVB receive an additional course of NB-UVB. Due to paucity of comparative data, retreatment (denoted with an orange box) is optional and the user can choose whether to allow these transitions in the model.

Patients begin treatment in the initial period; their response is assessed at week 52, unless treatment was discontinued due to any cause other than efficacy. Assessment of the initial response at week 52 enables the use of complete data from pooled TRuE-V Phase III studies[1] ensuring a fair comparison with NB-UVB. Given that the treatment duration of NB-UVB in the HI-Light study[4] was 9 months, and data for NB-UVB are unavailable beyond this timepoint, this health state considers the off-treatment period

before initiation of another course of NB-UVB. Initial response assessment at week 40 can be explored in a scenario analysis.

Responders transition to either the maintenance period health state or the stable health state. A responder is defined as a patient who achieves a response of F-VASI>25, as per Committee's suggestion to align with the SmPC of ruxolitinib cream. Patients who achieve F-VASI25-89 transition to the maintenance period health state and receive treatment; patients who achieve F-VASI90 transition to the stable health state where they no longer receive treatment, as validated by clinicians[6]. Non-responders, defined as F-VASI<25, transition to the non-response state to receive best supportive care (BSC) until death.

Response is reassessed at the end of the maintenance period (week 104). Following reassessment, patients achieving F-VASI25-89 remain in the maintenance state but stop treatment at week 104 and move to the non-response state at a constant rate. Patients achieving F-VASI90 transition to the stable health state and stop treatment. Patients whose F-VASI dropped to <25 transition to the non-response state where they receive BSC until death.

Patients remain in the stable health state until they experience a relapse, defined as F-VASI<75. Consistent with the clinical practice and the design of the TRuE-V LTE Cohort A study[6], patients who lose response have the option of retreatment and are modelled as transitioning to the retreated health state, where regaining F-VASI90 triggers transition to the 'stable retreated' state. All patients are retreated with ruxolitinib 1.5% cream regardless of whether they were initiated on ruxolitinib or no active treatment, in line with committee's preference. Patients initially treated with NB-UVB are retreated with two courses of NB-UVB. In the absence of efficacy data for retreatment with NB-UVB, the same efficacy as ruxolitinib 1.5% cream is conservatively assumed. Patients who do not wish to be retreated transition to the non-response health state.

The non-response health state receives patients who did not respond to their treatment by the end of the initial period (F-VASI<25), those who have discontinued treatment, as well as those who have not regained response following retreatment or

have lost a regained response. In the non-response state they receive BSC for lifetime, consistent with the NHSE clinical practice and the committee preference.

Patients can transition to the 'dead' state from all health states at any time according to the all-cause UK general population mortality[7], as per the original submission.

Clinical data used to inform the model transitions for each treatment sequence are provided in **Table 14**. Updates to the resource use inputs are described in Section 2.8.

2.5 Treatment periods in updated cost-effectiveness analysis

In the initial and the maintenance/retreatment periods, patients receiving ruxolitinib or no active therapy are treated continuously before response is assessed at week 52 and/or week 104, respectively (**Table 12**). A course of NB-UVB is received for 40 weeks (i.e., 9 months) in line with the draft guidance[8], resulting in a 3-month lag time between the end of treatment and assessment of response at week 52 and/or week 104. No patient receives treatment in the stable health state. Where patients are given the option of retreatment, a patient retreated with NB-UVB would be receiving their third course of therapy.

Table 12. Treatment periods in the base case analysis

Treatment	Initial period	Maintenance/retreatment period	Retreated
Ruxolitinib cream	Week 0-52	Week 52-104*	Following relapse from stable state until patients move to stable retreated or no response states***
No active treatment	Week 0-52	Week 52-104*	
NB-UVB	Week 0-40	Week 52-92**	

Abbreviations: NB-UVB: Narrowband ultraviolet B therapy.

*Continuous treatment for patients that initially responded at week 52. **Retreatment after a 3-month off-treatment period for patients that initially responded at week 52. ***For NB-UVB a one-year course of therapy is applied as a one-off cost.

2.6 Baseline characteristics

Patient baseline characteristics for the HI-Light and TRuE-V studies used in the cost-effectiveness analyses are presented below (**Table 13**):

Table 13. Baseline characteristics of populations considered in the analysis

Characteristic	HI-Light (N=169)		TRuE-V - Overall (N=674)	
	Mean value	SE	Mean value	SE
Age (years)	36.9	1.45	39.6	0.58
Weight (kg)	NA	NA	77.5	0.70
Female (%)	48	NA	53.1	0.02

Abbreviations: NA, not available; SE, standard error. Source: Incyte. Baseline characteristics of populations considered in the cost-effectiveness analyses [Data on file] [9].

2.7 Clinical data applied in the cost-effectiveness analysis

A definition of each model transition and data sources used to inform them are given in **Table 14**. Clinical data used to inform the transitions in the model are described in the following sections. All data and calculations are presented in Appendix B.

Table 14. Summary of transition definitions and data used to inform them.

Model Transition	Description	Data sources		Update from original submission
		Ruxolitinib vs no active treatment	Ruxolitinib vs NB-UVB	
Response	Defined as the proportion of patients in each respective arm achieving a response of F-VASI25 at 52 weeks (base case) or 40 weeks (scenario analysis).	Pooled TRuE-V1 and TRuE-V2 data (Phase III)[1]	MAIC estimates at week 40; transitions at week 104 are informed by risk ratios based on week 40 data	The original submission considered an (initial) response definition of F-VASI75 at week 24 in line with the primary endpoint of the TRuE-V Phase III studies[1]
Re-assessment of Response	Defined as the proportion of patients achieving one of two types of response at week 104: • F-VASI25-89: these patients remain in the maintenance/retreatment health state and move out to non-response at a constant rate • F-VASI90: these patients transition to the stable health state where they no longer receive treatment. Those with an F-VASI<25 transition to the non-response health state.	Cohort B TRuE-V LTE[2]. Risk ratios inform transitions for no active treatment based on the relative treatment effect estimated from the pooled TRuE-V[1] responses at week 24	Cohort B TRuE-V LTE[2]. Risk ratios are used to inform transitions for NB-UVB based on either the MAIC (base case) or the naïve comparison (scenario analysis) versus ruxolitinib	The original submission did not include a reassessment of response at the end of the maintenance period; sustained response defined as F-VASI90 was considered instead.

Model Transition	Description	Data sources		Update from original submission
		Ruxolitinib vs no active treatment	Ruxolitinib vs NB-UVB	
		(presented in Appendix B).	1.5% cream at week 40.	
Relapse	For the comparison of ruxolitinib 1.5% cream vs no active treatment and vs NB-UVB, this is defined as 'time to F-VASI<75' using data from the no active treatment arm of Cohort A in the TRuE-V LTE study. The 'no active treatment' data are utilised since the stable health state is an off-treatment state.	Cohort A TRuE-V LTE[2] study	Cohort A TRuE-V LTE[2] study	Unchanged from original submission
Regain Response (optional)	For the comparison of ruxolitinib 1.5% cream vs no active treatment, this is defined as 'time to regain response (F-VASI90) from the pooled data of no active treatment and ruxolitinib 1.5% cream arms of Cohort A in the TRuE-V LTE study[2]. For the comparison of ruxolitinib 1.5% cream vs NB-UVB, Cohort A TRuE-V LTE[2] data are used for ruxolitinib 1.5% cream, as above. In the absence of an appropriate source, these data are also used to define transitions for NB-UVB.	Cohort A TRuE-V LTE[2] study	Cohort A TRuE-V LTE[2] study	The original submission was informed by either ruxolitinib 1.5% cream or no active treatment data; this has now been updated to consider the pooled data as a conservative assumption
No Regain of Response (optional)	For the comparison of ruxolitinib 1.5% cream versus no active treatment, data is derived from the proportion of patients transitioning from F-VASI<75 at week 52 to F-VASI<90 at week 104 from Cohort B in the TRuE-V LTE study[2] from the no active treatment arm.	Cohort B TRuE-V LTE[2] study	Cohort B TRuE-V LTE[2] study	Unchanged from original submission

Model Transition	Description	Data sources		Update from original submission
		Ruxolitinib vs no active treatment	Ruxolitinib vs NB-UVB	
	For the comparison of ruxolitinib 1.5% cream versus NB-UVB, ruxolitinib 1.5% cream data as described above are used. For NB-UVB, the same data as above are applied given lack of data availability from HI-Light.			
No Response (optional)	In the absence of relapse data for previously re-treated patients who had achieved F-VASI90 and given that the same F-VASI definitions are used for both transitions, relapse data described above are used as a proxy for the 'no response' transition for the comparison of ruxolitinib 1.5% cream vs either no active treatment or NB-UVB.	Cohort A TRuE-V LTE[2] study	Cohort A TRuE-V LTE[2] study	Unchanged from original submission
Discontinuation/Dropout	**Comparison of ruxolitinib 1.5% cream vs no active treatment** *Initial period*: discontinuation data from pooled TRuE-V Phase III[1] studies *Maintenance/retreatment during the treatment period (up to week 104)*: discontinuation data from TRuE-V LTE[2] study Cohort B. *Maintenance/retreatment during off-treatment period (week>104)*: discontinuation data excluding AE and lack of efficacy from TRuE-V LTE[2] study Cohort B. **Comparison of ruxolitinib 1.5% cream vs NB-UVB** *On-treatment period:* Participants who discontinued NB-UVB from NB-UVB arm in HI-Light[4]	Pooled TRuE-V Phase III studies[1] and TRuE-V LTE Cohort B[2] data	HI-Light[4]	On- and off-treatment discontinuation/dropout rates are considered in the model

Model Transition	Description	Data sources		Update from original submission
		Ruxolitinib vs no active treatment	Ruxolitinib vs NB-UVB	
	Off-treatment period: Participants lost to follow-up in the follow up period from NB-UVB arm in HI-Light[4]			

Abbreviations: AE, adverse event; F-VASI, facial vitiligo area scoring index; F-VASI25, an improvement of 25% of greater from baseline; F-VASI<75, less than 75% improvement from baseline in F-VASI; F-VASI90, 90% or greater improvement from baseline in F-VASI; MAIC, matching-adjusted indirect comparison; NB-UVB, Narrowband ultraviolet B

2.7.1 Treatment response probabilities at 52 weeks

The proportion of patients achieving an initial response is used to define the transition from the initial period to the maintenance period/stable health state. Response is defined as the proportion of patients achieving F-VASI25 (i.e., ≥25% improvement from baseline in the face vitiligo area scoring index). Those achieving F-VASI90 transition directly to the stable health state.

2.7.1.1 Ruxolitinib 1.5% cream versus no active treatment

Overall, 55.34% of patients transition to the maintenance/retreatment period health state (F-VASI25-49: 11.24%, F-VASI50-74: 23.88% and F-VASI75-89: 20.22%). Patients achieving F-VASI90 (30.62%) transition to the stable health state where they no longer receive treatment. Finally, 14.04% of patients transition to the non-response health state to receive BSC[10,11] for the remainder of their lifetime.

Due to lack of efficacy data for no active treatment beyond week 24, no active treatment data are extrapolated from 24 to 52 weeks assuming the same response probability between the two timepoints.

For no active treatment, 28.91% of patients transition to the maintenance/retreatment period health state (F-VASI25-49: 11.37%, F-VASI50-74: 9.00% and F-VASI75-89: 8.53%). 1.90% of patients treated with no active treatment achieve F-VASI90 and transition to the stable health state, whereas 69.19% of patients do not achieve a response and transition to the non-response health state.

These data are based on an observed case analysis.

2.7.1.2 Ruxolitinib 1.5% cream versus NB-UVB

Week 40 modelled estimates (proportions) from the MAIC inform the response assessment at week 52 in the base case. Due to there being no F-VASI90 delineation in HI-Light, a simplifying assumption of 60% of patients achieving 75-100% falling into F-VASI75-89 was adopted, i.e., 40% achieving F-VASI90. The estimates used to inform the MAIC analysis and the naïve analysis in the cost-effectiveness model (CEM) are provided in **Table 5** in the ITC section.

2.7.2 Re-assessment of response probabilities at 104 weeks

In the maintenance/retreatment period patients stop ruxolitinib 1.5% cream and vehicle treatment at week 104 and NB-UVB at week 92 (i.e., 9 months of NB-UVB treatment). Re-assessment of response at week 104 determines transitions from the maintenance/retreatment period. All modelled patients are re-assessed and can either experience an improved response, a loss of response or response maintenance. Patients who maintain response stop receiving treatment and are modelled as moving out of maintenance/retreatment period at a constant dropout rate over time, thereby transitioning to the non-response health state. Patients achieving an F-VASI90 transition to stable state, whereas patients with F-VASI<25 transition to non-response.

2.7.2.1 Ruxolitinib 1.5% cream versus no active treatment

Cohort B data for participants initially (i.e., in TRuE-V up to week 24) allocated to ruxolitinib 1.5% cream and no active treatment from the TRuE-V LTE study[2] inform the transitions for ruxolitinib 1.5% cream. These data were used for the transition as they align with the updated assessment timepoint (i.e., 104 weeks). In the base case, shift summary data detailing response at week 104 for specific response thresholds at week 52 for ruxolitinib 1.5% cream (**Table 15**) and no active treatment (**Table 16**) were pooled together to calculate transition probabilities for ruxolitinib 1.5% cream to provide a more robust and precise evidence base.

Table 15. Shift summary of F-VASI from Week 52 to Week 104, ruxolitinib 1.5% cream. Cohort B, TRuE-V LTE[2]

Response at Week 52	n (%)	Response at week 104, n (%)					
		<F-VASI25	F-VASI 25-<50	F-VASI 50-<75	F-VASI 75-<90	F-VASI90	Missing
F-VASI 25-49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F-VASI 50-74	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F-VASI 75-89	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: F-VASI, facial vitiligo area scoring index; F-VASI25, 25% improvement from baseline in F-VASI; F-VASI50, 50% improvement from baseline in F-VASI; F-VASI75, 75% improvement from baseline in F-VASI; F-VASI90, 90% or greater improvement from baseline in F-VASI.
Source: Cohort B TRuE-V LTE [2]

Table 16. Shift summary of F-VASI from Week 52 to Week 104, no active treatment. Cohort B, TRuE-V LTE[2]

Response at Week 52	n (%)	Response at week 104, n (%)					
		<F-VASI25	F-VASI 25-<50	F-VASI 50-<75	F-VASI 75-<90	F-VASI90	Missing
F-VASI 25-49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F-VASI 50-74	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F-VASI 75-89	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: F-VASI, facial vitiligo area scoring index; F-VASI25, 25% improvement from baseline in F-VASI; F-VASI50, 50% improvement from baseline in F-VASI; F-VASI75, 75% improvement from baseline in F-VASI; F-VASI90, 90% or greater improvement from baseline in F-VASI.
Source: Cohort B TRuE-V LTE [2]

These data were used to determine the proportions of patients who have achieved F-VASI25-49, F-VASI50-74, F-VASI75-89 and F-VASI90 based on their response at week 52. Missing data are treated as non-responders in line with committee preference (i.e., they are assumed to have an F-VASI<25). The calculations are presented in Appendix B.

For no active treatment, due to lack of efficacy data beyond week 24, the relative effects from the response at week 24 compared to ruxolitinib 1.5% cream from the naïve comparison are applied to ruxolitinib 1.5% cream to inform transitions for patients treated with no active treatment (**Table 17**). For NB-UVB, the relative effects from the response at week 40 compared to ruxolitinib 1.5% cream from the MAIC comparison are applied to ruxolitinib 1.5% cream to inform transitions for patients treated with NB-UVB (**Table 17**).

Table 17. Week 24 naïve data used to inform risk ratios for no active treatment at week 104

Response	Modelled estimates-proportions ruxolitinib 1.5% cream – naïve comparison	Modelled estimates-proportions No active treatment – naïve comparison	Odds ratio*	Risk ratio†	Inverse risk ratio (No active vs ruxolitinib)
F-VASI 25-49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F-VASI 50-74	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F-VASI 75-89	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*calculated as (probability of ruxolitinib/(1-probability of ruxolitinib))/(probability of no active treatment/(1-probability of no active treatment)).

†calculated as probability ruxolitinib cream/probability no active treatment.

Source: Analysis of pooled TRuE-V studies [Data on file]

The inverse risk ratios applied to the ruxolitinib 1.5% cream data are calculated from the shift summary data in Table 15 to determine the proportion of responders at each threshold. Non-responders are calculated by subtracting the sum of the responders from one.

2.7.2.2 Ruxolitinib 1.5% cream versus NB-UVB

Data as given in **Table 18** are used to define transitions for ruxolitinib 1.5% cream. Due to a lack of data for NB-UVB at week 104, inverse risk ratios were calculated as per the above but using Week 40 MAIC data of ruxolitinib 1.5% cream versus NB-UVB in the calculations. Similarly, non-responders are calculated by subtracting the sum of the responders from one.

Table 18. Week 40 MAIC data used to inform risk ratios for NB-UVB at week 104

Response at week 104	Modelled estimates-proportions ruxolitinib 1.5% cream – MAIC	Modelled estimates-proportions no active treatment – MAIC	Odds ratio*	Risk ratio†	Inverse risk ratio (Vehicle vs ruxolitinib)
F-VASI 25-49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F-VASI 50-74	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F-VASI 75-100‡	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*calculated as (probability of ruxolitinib/(1-probability of ruxolitinib))/(probability of no active treatment/(1-probability of no active treatment))

†calculated as probability ruxolitinib cream/probability no active treatment

‡ applied to patients who achieved F-VASI-75-84 at week 52

Source: Analysis of pooled TRuE-V studies [Data on file]

2.7.3 Treatment relapse probabilities

Patients in the stable state have all achieved an F-VASI90 either at week 52 or at week 104. In line with natural history of the disease, patients may lose their response following cessation of treatment. When optional retreatment is not considered, these patients transition to the non-response health state. When optional retreatment is considered, these patients are retreated with the intervention to which they were initially allocated, in line with clinical feedback received during the appraisal committee meeting. The same relapse probabilities as per original submission are used, however, the user has the option to select ruxolitinib 1.5% cream data only, no active treatment data only or pooled (ruxolitinib 1.5% cream and no active treatment) from the TRuE-V LTE (Phase III)[2] to inform the transition. The no active treatment data are used in the base case.

2.7.3.1 Ruxolitinib 1.5% cream versus no active treatment

The transition from stable to the non-response or the re-treated health state is informed by time-to-relapse data (i.e., time to F-VASI<75) from the ruxolitinib 1.5% cream arm of Cohort A in the TRuE-V LTE study[2]. Patients in Cohort A were randomised to either ruxolitinib 1.5% cream or no active treatment and followed up between week 52 and week 104. Relapse data from the no active treatment arm of

Cohort A informs transitions to either non-response or retreated. This is reflective of the stable health state not being associated with any treatment, as patients stop treatment upon transitioning to stable state. These data are applied to both the ruxolitinib 1.5% cream and no active treatment arms.

2.7.3.2 Ruxolitinib 1.5% cream versus NB-UVB

The ruxolitinib 1.5% cream data are derived in the same manner as described above for the comparison with no active treatment. As the stable health state is considered a treatment-agnostic state and given the absence of data related to relapse for NB-UVB from HI-Light, the transition of NB-UVB patients to the non-response or retreated health state is assumed equal to that of no active treatment and ruxolitinib 1.5% cream (i.e., no active treatment data inform the transition).

2.7.4 Retreatment

No updates were made to the data informing the retreatment phase of the cost-effectiveness model. However, the user may choose between ruxolitinib 1.5% cream data, no active treatment data or pooled data from the LTE study for the regain response input. Pooled data is used in the company base case.

2.7.5 Discontinuation and dropout

Discontinuation (during the on-treatment periods) and dropout (during the off-treatment periods) rates are presented in **Table 19** and **Table 20**. As per the original submission, no discontinuation is assumed in the optional re-treated health state for both the intervention and comparator as the no regain response transition acts as a proxy for discontinuation. This is based on the assumption that patients will continue treatment until it either produces an effect or fails to do so.

Treatment-specific discontinuation rates were derived from the pooled data of the TRuE-V studies[1] and were converted to a per-cycle transition probability. During the initial period, discontinuation rates account for all causes except lack of efficacy, based on data from week 0 to 52. In contrast, discontinuation rates during the maintenance period relate to all causes, including lack of efficacy, as informed by data from Cohort B from the TRuE-V LTE study[2]. Given that the discontinuation/dropout rates from week

24 onwards are from patients that either switched from no active treatment to ruxolitinib 1.5% cream or the ruxolitinib 1.5% arm per se, the discontinuation/dropout estimates for no active treatment in the model represent a conservative assumption.

For NB-UVB discontinuation/dropout, data for the on- and off-treatment periods were obtained from the HI-Light study[4]. Discontinuation for the on-treatment period is taken from the participants who discontinued NB-UVB during the 9-month treatment phase in the NB-UVB arm (47/169 = 27.81%). Dropout for the off-treatment period is taken from the follow-up period (month 9 to month 21) in the NB-UVB arm [(123-72)/123 = 41.46%] (**Table 20**). All discontinuation/dropout rates were converted to cycle-specific probabilities.

Table 19. Discontinuation/dropout rates for ruxolitinib and no active treatment

Timepoint	Ruxolitinib cream	No active treatment	Source
Week 0-52	[redacted]	[redacted]	Pooled TRuE-V Phase III studies[1] week 0-52 all-cause discontinuation excluding lack of efficacy
Week 52-104	[redacted]	[redacted]	TRuE-V LTE study Cohort B[2] all-cause discontinuation
Week>104	[redacted]	[redacted]	TRuE-V LTE study Cohort B[2] all-cause discontinuation excluding adverse event and lack of efficacy

Abbreviations: TRuE-V, topical ruxolitinib evaluation in vitiligo long-term extension study; LTE, long-term extension.

Table 20. Discontinuation/dropout rates for NB-UVB

Timepoint	NB-UVB	Source
On treatment (week 0-40, week 52-92)	27.81%	HI-Light study, participants who discontinued NB-UVB monotherapy in the NB-UVB monotherapy arm (Table 5 HI-Light HTA report)[4]
Off treatment	41.46%	HI-Light study, participants followed-up from 9 months to 21 months (Figure 2 HI-Light HTA report)[4]

Abbreviations: Hi-Light, home intervention of light therapy trial; HTA, health technology assessment; NB-UVB, narrow band ultraviolet B.

2.7.6 Adverse events

As stated in the original submission, a very low incidence of serious TEAEs was observed in the TRuE-V1 and TRuE-V2 trials during the double-blind period of 24 weeks (2.1% and 0.6% of participants had a serious TEAE across both treatments from the TRuE-V1 and TRuE-V2 trials, respectively).[12] The committee stated a preference for adverse events occurring in ≥1% of patients in each treatment arm to be considered in the cost-effectiveness analysis, including cost and disutility. Data provided in **Table 21** and **Table 22** demonstrate that adverse events occurring in ≥1% of patients treated with ruxolitinib 1.5% cream are mild and transient, while patients treated with NB-UVB experience a large number of erythema events.

Table 21. Adverse events occurring in ≥1% of pooled TRuE-V study participants during 24-weeks

Adverse event	Ruxolitinib 1.5% cream- number of events (N=449)	Rates of related AEs (SE)	No active treatment – number of events (N=224)	Rates of related AEs (SE)
Alanine aminotransferase increased	5	0.011136 (0.005)	2	0.008929 (0.006)
Application site acne	28	0.062361 (0.011)	3	0.013393 (0.008)
Application site erythema	7	0.015590 (0.006)	1	0.004464 (0.005)
Application site exfoliation	5	0.011136 (0.005)	3	0.013393 (0.008)
Application site pruritus	29	0.064588 (0.012)	8	0.035714 (0.012)
Application site rash	7	0.015590 (0.006)	2	0.008929 (0.006)
Arthralgia	3	0.006682 (0.004)	3	0.013393 (0.008)
COVID-19	14	0.031180 (0.008)	7	0.031250 (0.012)
Dysmenorrhoea	6	0.013363 (0.005)	0	0.000000 (0.000)
Headache	25	0.055679 (0.011)	6	0.026786 (0.011)
Hypertension	5	0.011136 (0.005)	0	0.000000 (0.000)
Influenza	6	0.013363 (0.005)	1	0.004464 (0.005)
Nasopharyngitis	20	0.044543 (0.010)	5	0.022321 (0.010)

Adverse event	Ruxolitinib 1.5% cream-number of events (N=449)	Rates of related AEs (SE)	No active treatment – number of events (N=224)	Rates of related AEs (SE)
Oral herpes	7	0.015590 (0.006)	4	0.017857 (0.009)
Pharyngitis streptococcal	0	0.000000 (0.000)	3	0.013393 (0.008)
Pyrexia	8	0.017817 (0.006)	0	0.000000 (0.000)
Sinusitis	10	0.022272 (0.007)	5	0.022321 (0.010)
Upper respiratory tract infection	15	0.033408 (0.009)	5	0.022321 (0.010)
Urinary tract infection	6	0.013363 (0.005)	1	0.004464 (0.005)

Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; SE, standard error; TRuE-V, topical ruxolitinib evaluation study.

Source: Analysis of pooled TRuE-V studies [Data on file]

Table 22. Adverse events occurring in ≥1% of participants randomised to NB-UVB in HI-Light during 9 months**

Adverse Event	HI-Light NB-UVB arm Number of events (N=169)	Rate (SE)
Acne	1	0.0059 (0.006)
Application site pruritus	2	0.0118 (0.008)
Blister	4	0.0237 (0.012)
Contusion	0	0.0000 (0.000)
Dry skin	0	0.0000 (0.000)
Erythema	29	0.1716 (0.030)
Folliculitis	0	0.0000 (0.000)
Haemangioma	1	0.0059 (0.006)
Hair growth abnormal	2	0.0118 (0.008)
Herpes virus infection	2	0.0118 (0.008)
Herpes zoster infection	0	0.0000 (0.000)
Koebner phenomenon	1	0.0059 (0.006)
Lip dry	0	0.0000 (0.000)
Lip pain	0	0.0000 (0.000)
Melanocytic naevus	1	0.0059 (0.006)
Miliaria	0	0.0000 (0.000)
Night sweats	1	0.0059 (0.006)
Oral discomfort	0	0.0000 (0.000)
Oral herpes	4	0.0237 (0.012)
Pain in extremity	0	0.0000 (0.000)
Pain in jaw	0	0.0000 (0.000)
Pain of skin	0	0.0000 (0.000)
Paraesthesia	0	0.0000 (0.000)

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Adverse Event	HI-Light NB-UVB arm Number of events (N=169)	Rate (SE)
Polymorphic light eruption	1	0.0059 (0.006)
Pruritus	7	0.0414 (0.020)
Pustular psoriasis	0	0.0000 (0.000)
Rash	3	0.0178 (0.010)
Rash pruritic	2	0.0118 (0.008)
Rhinalgia	0	0.0000 (0.000)
*Skin atrophy	1	0.0059 (0.006)
Skin depigmentation	0	0.0000 (0.000)
Skin exfoliation	5	0.0296 (0.013)
Skin hyperpigmentation	0	0.0000 (0.000)
Skin papilloma	0	0.0000 (0.000)
*Skin striae	0	0.0000 (0.000)
*Spider vein	1	0.0059 (0.006)
*Telangiectasia	0	0.0000 (0.000)
Vitiligo	1	0.0059 (0.006)

Abbreviations: Hi-Light, home intervention of light therapy trial; NB-UVB, narrow band ultraviolet B; SE, standard error.
*Skin thinning was defined as any events classified as skin atrophy, skin striae, telangiectasia or spider vein. **9 months assumed to be 40 weeks. Source: Batchelor et al., 2020; Table 17[4]

In line with the original submission, the company included the cost impact of the following adverse events: acne (including application site), pruritis (including application site), nasopharyngitis, headache, upper respiratory tract infection. The following AEs were amongst the most frequent for NB-UVB and are included in the revised CEM for all treatments for consistency: erythema (including application site), skin exfoliation and skin thinning. It is assumed that patients will seek a dermatologist consultation for erythema, skin exfoliation and skin thinning.

Disutility was not included, partly due to lack of HRQoL estimates for such AEs in vitiligo or other dermatological conditions and partly due to the minimum impact this is anticipated to have in the results. The rates of these adverse events applied in the cost-effectiveness analysis are presented in **Table 23**.

Table 23. Adverse event rates applied in the cost-effectiveness model

Adverse Event	Ruxolitinib 1.5% cream	No active treatment	NB-UVB
Acne (incl. application site)	6.24%	1.34%	0.59%
Pruritus (incl. application site)	6.46%	3.57%	5.33%

Adverse Event	Ruxolitinib 1.5% cream	No active treatment	NB-UVB
Nasopharyngitis	4.45%	2.23%	0.00%
Headache	5.57%	2.68%	0.00%
Upper respiratory tract infection	3.34%	2.23%	0.00%
Erythema (incl. application site)	1.56%	0.45%	17.16%
Skin exfoliation	0.00%	0.00%	2.96%
Skin thinning	0.00%	0.00%	1.18%

Abbreviations: NB-UVB, narrow band ultraviolet B.

Source: Analysis of adverse events from TRuE-V studies and HI-Light [Data on file]

2.8 Resource use

The Company acknowledge the feedback received from the committee regarding resource use for vitiligo expected in clinical practice. In line with this feedback, the Company updated their resource use assumptions. Updates have been made to the following categories:

- Drug acquisition costs
- Disease management resource use

The following sections describe the changes.

2.8.1 Drug acquisition costs

2.8.1.1 Intervention and comparator

No active treatment

Considering the committee feedback, the Company updated the cost of no active treatment to be £0. There are no changes to pack size, daily dose, dose frequency, or doses required.

Ruxolitinib 1.5% cream

Updates to the ruxolitinib dosage data are described in the ACD response document (comment number 6).

NB-UVB

The costing of NB-UVB remains unchanged. To summarise, patients undergo three sessions per week for 9 months resulting in 120 sessions for one course (assuming that 9 months is equal to 40 weeks). Patients undertake a course in the initial period and in the maintenance/retreatment periods, respectively. In the optional retreatment phase a one-off cost for two NB-UVB courses is applied. Although clinicians described that patients may undergo NB-UVB for around 12 months, the company consider 9 months to be a conservative approach in alignment with the HI-Light study. Hospital-based NB-UVB is assumed to have equal efficacy to the home-based NB-UVB have equal efficacy (**Table *28***). As per original submission, the cost of £140.84 per session is based on 'Outpatient dermatology procedure tariff (JC47Z)', in line with TA534[14] and TA681[15].

2.8.1.2 Best supportive care basket

Resource use and cost elements in BSC, as received by patients in the non-response health state, are unchanged with the exception of NB-UVB.

- In the comparison of ruxolitinib 1.5% cream versus no active treatment, either 0% or 25% of patients receive NB-UVB for two years (i.e., approximately two courses) in the non-response health state.
- In the comparison of ruxolitinib 1.5% cream versus NB-UVB, no patients receive NB-UVB in the non-response health state.

The costing for NB-UVB is as described in Section 2.8.1.1. In BSC, the model only considers hospital-based NB-UVB as home-based phototherapy is limited to 1-2 centres in the UK and is therefore not reflective of phototherapy usage in the UK, as per clinician feedback[16]. Patients receive the remaining components of BSC for a lifetime in line with the Committee's suggested approach.

2.8.2 Disease management costs

During the committee meeting, the clinicians described the resource constraints experienced by dermatology departments in England for psychological support. However, the committee accepted the EAG assumption that 15% of patients would

receive psychological support irrespective of health state. The Company updated their model to reflect 15% of patients receiving psychological support in clinical practice across all health states.

Additionally, resource use in the non-response health state was updated as described in **Table 24**. No changes were made to the costing of resource use in the cost-effectiveness analysis.

Table 24. Updates to resource use in non-response health state

Parameter	Resource Use	Justification
Phototherapy	25% of patients receive NB-UVB; applied only in comparison with no active treatment	In line with draft guidance[8]
Dermatology appointments	One appointment every six months for two years	As per clinical validation, the company have retained current values in all health states but assumed patients considered non-responders have reduced and limited resource use
Dermatology nurse visit	This has been set to zero	As per clinical validation, the company have retained current values in all health states but assumed patients considered non-responders do not have any nurse visits
Dermatology telephone appointment	This has been set to zero	As per clinical validation, the company have retained current values in all health states but assumed patients considered non-responders do not have any telephone appointments
Duration of costs in non-response	Costs last for the whole time in the non-response health state	In line with draft guidance

Abbreviations: NB-UVB, narrow band ultraviolet B.

The resource use in each health state, where this has been updated, is provided in **Table 25**.

Table 25. Disease management resource use and costs

Resource use item	Resource use input per cycle	SE	Source	Unit cost (unchanged)	Source (unchanged)
Initial, maintenance periods and retreated					
Psychological support	0.150	0.02	Draft guidance[8]	£344.21	NHS Reference Costs; weighted average of WF01A–D[17]
Stable disease and stable retreated states					
Psychological support	0.150	0.02	Draft guidance[8]	£344.21	NHS Reference Costs; weighted average of WF01A–D[17]
Non-response state					
Dermatologist outpatient consultation	0.150	0.02	Draft guidance[8]	£155.40	NHS Reference Costs; WAVG of WF01A-D and WF02A-C[17]
Dermatologist telephone appointment	0	0		£115.44	NHS Reference Costs; WF01C[17]
Dermatologist nurse visit	0	0		£17.00	PSSRU; per patient contact lasting 15 minutes[18]
GP consultation	0.012	0.001		£42.00	PSSRU; per patient contact lasting 9.22 minutes[18]
A&E visit	0.010	0.001		£220.65	NHS Reference Costs; WAVG of VB06Z-09Z[17]
Psychological support	0.150	0.02		£344.21	NHS Reference Costs; weighted average of WF01A–D[17]

Abbreviations: A&E, accident and emergency department; GP, general practitioner; NHS, National Health Service; PSSRU, Personal Social Services Research Unit; SE, standard error; WAVG, weighted average.

2.9 Health-related quality of life

Utilities for patients treated with NB-UVB in HI-Light are not available by repigmentation score. The Company applied their previous methods as described in the original submission, and accepted by the committee, to develop treatment-agnostic response-based utility values for application to all comparators in the cost-effectiveness analysis.

2.9.1 Application of mapping algorithms to pooled TRuE-V data at week 24

The algorithms were applied to the ITT population to estimate the change from baseline utility based on response observed: F-VASI25, F-VASI50, F-VASI-75, F-VASI90 and non-responder. The analysis relies on the assumption that RPS is an appropriate proxy for F-VASI due to the notable similarities in the methods of measurement as previously described.

The change from baseline estimates were applied to the baseline value (i.e., 0.881) to estimate the utility value for each response level as presented in Table 27. The higher estimated utility change from baseline value of F-VASI25-49 response compared with the value of F-VASI50-74 (Table 26) may be attributed to the inability to discriminate the difference in quality of life between the F-VASI25-49 and F-VASI50-74 response categories.

Table 26. Utility change from baseline values by response

Response	Change from baseline: mean (standard error)	95% CI (Lower: Upper)
Baseline*	0.881 (0.002)	0.877: 0.885
No response	-0.123 (0.003)	-0.128, -0.117
F-VASI25-49	0.035 (0.009)	0.016, 0.053
F-VASI50-74	0.011 (0.009)	-0.006, 0.028
F-VASI75-89	0.054 (0.010)	0.034, 0.073
F-VASI90	0.072 (0.010)	0.052, 0.092

*Included in algorithm
Abbreviations: F-VASI, facial vitiligo area scoring index; F-VASI25-49 25% to 49% improvement from baseline in F-VASI; F-VASI50-74, 50% to 74% improvement from baseline in F-VASI; F-VASI75-89, 75% to 89% improvement from baseline in F-VASI; F-VASI90, 90% or greater improvement from baseline in F-VASI.
Source: Incyte, technical report for statistical analysis and utility modelling [Data on file][20]

Table 27. Health state utility values by response

Response (health state)	Utility value: mean
Baseline* (initial period, retreated)	0.881
No response (non-response state)	0.758
F-VASI25-49 (maintenance/ retreatment period)	0.915
F-VASI50-74 (maintenance/ retreatment period)	0.892
F-VASI75-89 (maintenance/ retreatment period)	0.934
F-VASI90 (stable, stable retreated)	0.953

*Included in algorithm

Abbreviations: F-VASI, facial vitiligo area scoring index; F-VASI25-49 25% to 49% improvement from baseline in F-VASI; F-VASI50-74, 50% to 74% improvement from baseline in F-VASI; F-VASI75-89, 75% to 89% improvement from baseline in F-VASI; F-VASI90, 90% or greater improvement from baseline in F-VASI.
Source: Incyte, technical report for statistical analysis and utility modelling [Data on file] [20]

The Company note that the committee preferred the EAG approach of weighting utilities in non-response based on a weighted average of no response and F-VASI 50 to 74 values in ruxolitinib arm at 24 weeks. This adjustment is no longer applicable to the base case analysis where the initial response definition is set to F-VASI25. However, when the user selects a higher response level, weighting is applied and the user can choose to weight non-response utilities based on either ruxolitinib 1.5% cream, the selected comparator or the pooled data from both ruxolitinib cream and the selected comparator.

2.10 Cost-effectiveness analysis assumptions

Assumptions in the updated cost-effectiveness analysis are described in **Table 28**.

Table 28. Cost-effectiveness analysis assumptions

Assumption	Detail and Justification
Treatment in the initial period	Patients who are treated with either ruxolitinib 1.5% cream or no active treatment receive treatment for 52 weeks in the initial period. Patients receiving NB-UVB are treated for 40 weeks (i.e., 9 months) following which they cease treatment and experience a 3-month off-treatment period. Assessment of initial response occurs once at week 52. This is in line with the TRuE-V Phase III studies[1] and the HI-Light trial.[3] The off-treatment period for NB-UVB aligns with clinical practice.[6]
Patient transition from the initial period to the stable health state	Patients who achieve F-VASI90 at week 52 move directly to the stable health state and stop receiving treatment. This is in line with the TRuE-V long-term extension study[2] and clinician feedback.[6]
Relapse	Patients who lose F-VASI75 response in stable state either directly transition to the non-response health state (retreatment not selected) or transition to the retreatment health states (retreatment selected). This is in line with the TRuE-V long-term extension study[2] and clinician feedback.[6]
Relapse data source	The same relapse rates are used for all modelled treatments (ruxolitinib 1.5% cream, no active treatment and NB-UVB) since all patients irrespective of treatment received are off treatment in the stable state.
Maintenance/retreatment health state	In the maintenance period/retreatment health state, patients receiving ruxolitinib 1.5% cream or no active treatment continue receiving treatment (up to week 104), whereas patients receiving NB-UVB are assumed to be retreated for another 9 months (up to week 92). At week 104 all patients are re-assessed and can improve response, lose response, or maintain response. Patients who maintain response stop receiving treatment and move to non-response at a constant dropout rate over time. Patient who achieve F-VASI90 move to stable health state and patients with F-VASI<25 move to non-response health state. This is in line with the TRuE-V long-term extension study[2] and HI-Light[3]. Clinician feedback provided in the draft guidance stated that patients receiving NB-UVB would undergo two courses of treatment lasting around 9-12 months each.[8]

Assumption	Detail and Justification
Retreatment health states	In the optional retreatment health states, in the absence of efficacy data for no active treatment and NB-UVB, efficacy is assumed equal to that of ruxolitinib 1.5% cream.
NB-UVB efficacy and costing	The efficacy of home-based and hospital-based NB-UVB is assumed equal; hospital-based costing is applied to NB-UVB.
NB-UVB initial response	Week 40 data for NB-UVB is applied to the assessment of initial response at week 52 assuming a flat extrapolation. This assumes that there is no loss of efficacy from week 40 to week 52.
Assessment of response at week 104	In the absence of efficacy data for NB-UVB and no active treatment, risk ratios are calculated using week 40 matching-adjusted indirect comparison data for NB-UVB (due to lack of head-to-head data) and week 24 naïve comparison for no active treatment (due to available head-to-head data from TRuE-V studies), respectively, and applied to ruxolitinib 1.5% cream data to derive relative efficacy estimates.
Discontinuation	In the absence of data, the same discontinuation data are used in maintenance between week 52-104 (on treatment) and after 104 (off treatment).
Comparative efficacy	NB-UVB response 75-100 will be split between 75-90 and 90-100 assuming a 60:40 split between the 2 categories due to lack of break down by response categories used in the CEM. This is a user-defined setting in the model.
Comparative efficacy	The overall population from the TRuE-V studies was matched to reflect the baseline characteristics of the Hi-Light study. This assumes that the populations in the 2 RCTs are sufficiently similar and the impact of any disease prognostic or effect modifying factors has been accounted for in the matching process

Abbreviations: CEM, cost-effectiveness model; F-VASI, facial vitiligo area scoring index; Hi-Light, home intervention light therapy trial; NB-UVB, narrow band ultraviolet B; TRuE-V, topical ruxolitinib evaluation study.

3 Results

3.1 Comparison with NB-UVB

3.1.1 Deterministic cost-effectiveness results

The deterministic cost-effectiveness results for the comparison with NB-UVB are presented in **Table 29**. For all analyses, ruxolitinib cream was considered at its confidential PAS price. When compared to NB-UVB, ruxolitinib cream produces an additional [redacted] QALYs with an incremental cost of [redacted], resulting in a net monetary benefit (NMB) of £18,355. On average, patients on ruxolitinib cream spent 0.831 years in F-VASI90 (i.e., stable and stable retreated) compared with 0.126 years in patients on NB-UVB. These results indicate that ruxolitinib cream is dominant versus NB-UVB for the overall population of adult and adolescent patients >12 years of age with non-segmental vitiligo.

Table 29. Deterministic summary results at PAS price, comparison with NB-UVB

Technologies	Total time in F-VASI90 (years)	Total costs (£)	Total QALYs	Incremental time in F-VASI90 (years)	Incremental costs (£)	Incremental QALYs	NMB versus baseline (QALYs)
NB-UVB	0.126	[redacted]	[redacted]	-	-	-	-
Ruxolitinib cream	0.831	[redacted]	[redacted]	0.705	[redacted]	[redacted]	£18,355

Abbreviations: F-VASI90, 90% or greater improvement from baseline in Facial Vitiligo Area Scoring Index; NB-UVB, Narrowband ultraviolet B; NMB, Net monetary benefit; QALY, Quality-adjusted life year

3.1.2 Probabilistic sensitivity analysis

Joint parameter uncertainty was tested through PSA, in which all parameters are assigned distributions and varied jointly. 1,000 Monte Carlo simulations were recorded and plotted on the cost-effectiveness plane shown in **Figure 6** below. The results of the PSA were found to be congruent with the base-case results. Results showed that 100.0% of samples lie in the south-east quadrant where the target intervention is dominant over NB-UVB. The probability of cost-effectiveness for ruxolitinib cream at WTP threshold of £20,000 was found to be [redacted] at PAS price.

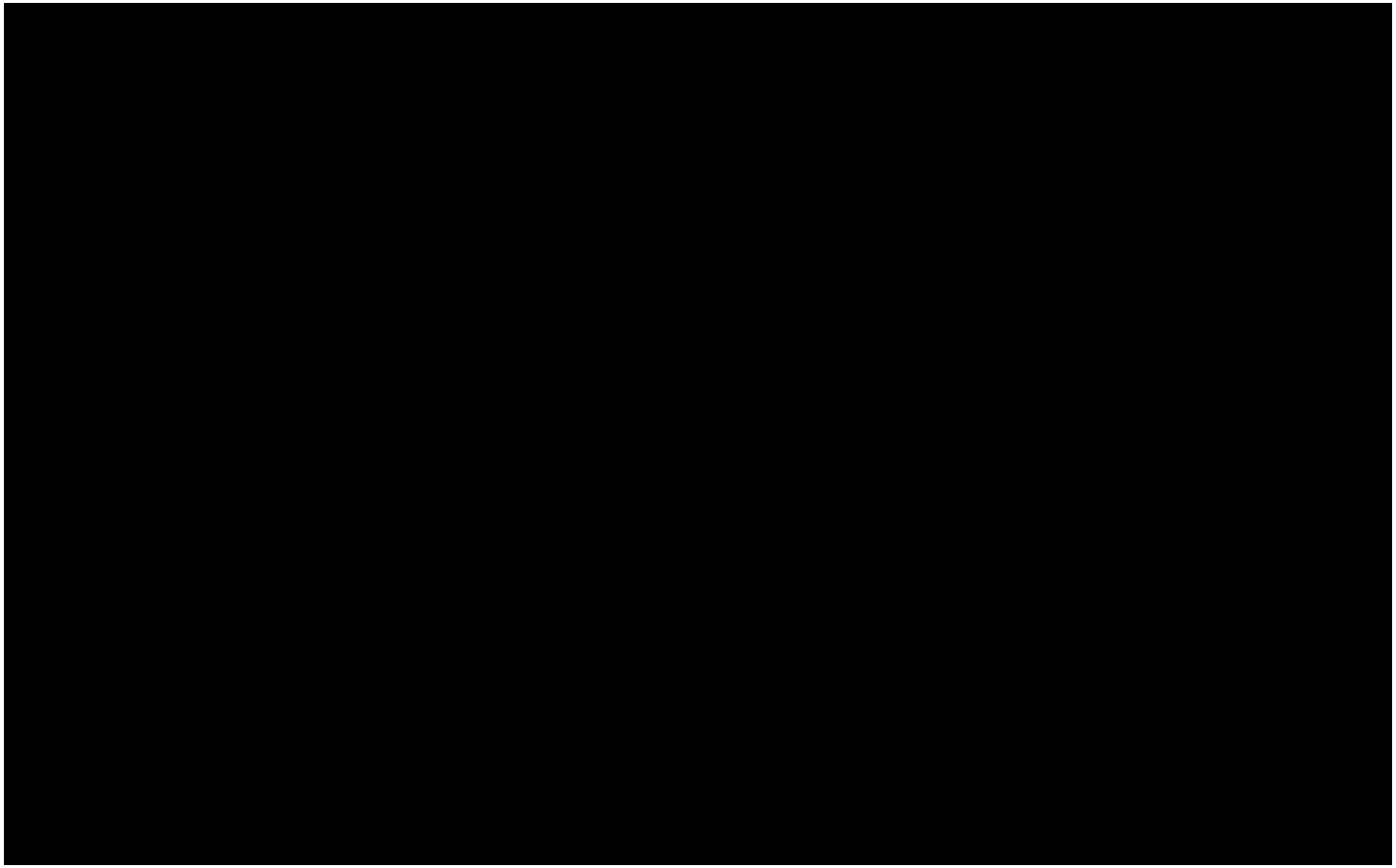
Figure 6. Cost-effectiveness plane for ruxolitinib cream compared with NB-UVB at PAS price

Abbreviations: PSA, probabilistic sensitivity analysis; QALYs, quality adjusted life years; WTP, willingness to pay.

3.1.3 Deterministic sensitivity analysis

Deterministic (one-way) sensitivity analysis was performed, and the 20 most important drivers of the model were plotted in a tornado diagram (**Figure 7**). The most influential parameter for the analysis of ruxolitinib cream versus NB-UVB was the on-treatment discontinuation rate for NB-UVB, followed by the post-treatment discontinuation rate for ruxolitinib cream during the maintenance period. The initial F-VASI50-74 and F-VASI25-49 response rates for NB-UVB were also found to be influential.

Figure 7. Tornado diagram for ruxolitinib cream compared with NB-UVB at PAS price



Abbreviations: F-VASI, facial vitiligo area scoring index; MAIC, matching adjusted indirect comparison; NB-UVB, narrow band ultraviolet B; NMB, net monetary benefit; OWSA, one way sensitivity analysis; QALYs, quality adjusted life years; RU, resource utilisation.

3.2 Comparison with NB-UVB & TCS

The deterministic cost-effectiveness results for the comparison with NB-UVB & TCS are presented in **Table 30**. When compared to NB-UVB & TCS, ruxolitinib cream produces an additional [redacted] QALYs with an incremental cost of [redacted], resulting in an NMB of £18,718. On average, patients on ruxolitinib cream spent 0.829 years in F-VASI90 (i.e., stable and stable retreated) compared with 0.190 years in patients on NB-UVB & TCS. These results indicate that ruxolitinib cream is dominant versus NB-UVB & TCS for the overall population of adult and adolescent patients >12 years of age with non-segmental vitiligo.

Table 30. Deterministic summary results at PAS price, comparison with NB-UVB & TCS

Technologies	Total time in F-VASI90 (years)	Total costs (£)	Total QALYs	Incremental time in F-VASI90 (years)	Incremental costs (£)	Incremental QALYs	NMB versus baseline (QALYs)
NB-UVB & TCS	0.190	[redacted]	[redacted]	-	-	-	-
Ruxolitinib cream	0.829	[redacted]	[redacted]	0.639	[redacted]	[redacted]	£18,718

Abbreviations: F-VASI90, 90% or greater improvement from baseline in Facial Vitiligo Area Scoring Index; NB-UVB, Narrowband ultraviolet B; NMB, Net monetary benefit; TCS, Topical corticosteroid; QALY, Quality-adjusted life year

3.3 Comparison with no active treatment followed by NB-UVB

3.3.1 Deterministic cost-effectiveness results

The base-case probabilistic cost-effectiveness results are presented in **Table 31**. When compared to no active treatment followed by NB-UVB, ruxolitinib cream produces an additional [redacted] QALYs with an incremental cost of [redacted], resulting in an ICER of £18,103. On average, patients on ruxolitinib cream spent 1.039 years in F-VASI90 (i.e., stable and stable retreated) compared with 0.119 years in patients on no active treatment followed by NB-UVB. These results indicate that ruxolitinib cream is cost-effective versus no active

treatment followed by NB-UVB at a cost-effectiveness threshold of £20,000 for the overall population of adult and adolescent patients >12 years of age with non-segmental vitiligo.

Table 31. Deterministic summary results at PAS price, comparison with no active treatment followed by NB-UVB

Technologies	Total time in F-VASI90 (years)	Total costs (£)	Total QALYs	Incremental time in F-VASI90 (years)	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
No active treatment followed by NB-UVB	0.119	[redacted]	[redacted]	-	-	-	-
Ruxolitinib cream	1.039	[redacted]	[redacted]	0.920	[redacted]	[redacted]	£18,103

Abbreviations: F-VASI90, 90% or greater improvement from baseline in Facial Vitiligo Area Scoring Index; ICER, Incremental cost-effectiveness ratio; NB-UVB, Narrowband ultraviolet B; QALY, Quality-adjusted life year

3.3.2 Probabilistic sensitivity analysis

Joint parameter uncertainty was tested through PSA, in which all parameters are assigned distributions and varied jointly. 1,000 Monte Carlo simulations were recorded and plotted on the cost-effectiveness plane shown in **Figure 8** below. The results of the PSA were found to be congruent with the base-case results. Results showed that 100.0% of samples lie in the north-east quadrant where the target intervention is more costly and more effective compared with no active treatment followed by NB-UVB. The probability of cost-effectiveness for ruxolitinib cream at WTP thresholds of £20,000 and £30,000 was found to be [redacted] and [redacted] at PAS price, respectively, as shown in the cost-effectiveness acceptability curve (CEAC) in **Figure 9** below.

Figure 8. Cost-effectiveness plane for ruxolitinib cream compared with no active treatment followed by NB-UVB at PAS price

Abbreviations: NB-UVB, narrow band ultraviolet B; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALYs, quality adjusted life years; WTP, willingness to pay.

Figure 9. Cost-effectiveness acceptability curve for ruxolitinib cream compared with no active treatment at PAS price

Abbreviations: PAS, patient access scheme.

3.3.3 Deterministic sensitivity analysis

Deterministic (one-way) sensitivity analysis was performed, and the 20 most important drivers of the model were plotted in a tornado diagram (**Figure 10**). The most influential parameter for the analysis of ruxolitinib cream versus no active treatment followed by NB-UVB was the post-treatment discontinuation rate for ruxolitinib cream during the maintenance period, followed by the relapse rate for ruxolitinib cream. The initial F-VASI90 response and no regain response rates for ruxolitinib cream were also found to be influential.

Figure 10. Tornado diagram for ruxolitinib cream compared with no active treatment followed by NB-UVB at PAS price

Abbreviations: F-VASI, facial vitiligo area scoring index; ICER, incremental cost effectiveness ratio; NB-UVB, narrow band ultraviolet B; PAS, patient access scheme; OWSA, one way sensitivity analysis; RU, resource utilisation.

3.3.4 Scenario analyses

Uncertainty around the average daily dose of ruxolitinib cream was tested in scenario analyses. The scenario analyses carried out and their respective results are presented below in **Table 32** for the confidential PAS price.

Table 32. Summary of key cost-effectiveness results from scenario analyses at PAS price

No	Model scenario	Average daily dose of ruxolitinib cream	Treatment	Total costs (£)	Incremental Costs (£)	ICER versus baseline (£/QALY)
-	Base case: Applying lognormal distribution to TRuE-V data	Mean of 3.84g	No active treatment followed by NB-UVB	[redacted]	-	-
			Ruxolitinib cream	[redacted]	[redacted]	£18,103
1	Observed TRuE-V data	Median of 4.03g	No active treatment followed by NB-UVB	[redacted]	-	-
			Ruxolitinib cream	[redacted]	[redacted]	£19,011
2	TRuE-V data excluding 9 patients with outliers	Mean of 4.53g	No active treatment followed by NB-UVB	[redacted]	-	-
			Ruxolitinib cream	[redacted]	[redacted]	£21,400
3	Estimated mean from VALIANT	Mean of 2.23g	No active treatment followed by NB-UVB	[redacted]	-	-
			Ruxolitinib cream	[redacted]	[redacted]	£10,411

Abbreviations: ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year; TRuE-V, topical ruxolitinib evaluation study; VALIANT, the Vitiligo and Life Impact Among International Communities study.

3.4 Comparison with no active treatment

The base-case probabilistic cost-effectiveness results are presented in **Table 33**. When compared to no active treatment, ruxolitinib cream produces an additional [redacted] QALYs with an incremental cost of [redacted], resulting in an ICER of £20,018. On average, patients on

ruxolitinib cream spent 1.039 years in F-VASI90 (i.e., stable and stable retreated) compared with 0.119 years in patients on no active treatment. These results indicate that the ICER of ruxolitinib cream versus no active treatment is slightly above the cost-effectiveness threshold of £20,000 for the overall population of adult and adolescent patients >12 years of age with non-segmental vitiligo.

Table 33. Deterministic summary results at PAS price, comparison with no active treatment

Technologies	Total time in F-VASI90 (years)	Total costs (£)	Total QALYs	Incremental time in F-VASI90 (years)	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
No active treatment	0.119	[redacted]	[redacted]	-	-	-	-
Ruxolitinib cream	1.039	[redacted]	[redacted]	0.920	[redacted]	[redacted]	£20,018

Abbreviations: F-VASI90, 90% or greater improvement from baseline in Facial Vitiligo Area Scoring Index; ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year

4 Discussion

4.1 Summary of cost-effectiveness evidence

Results of the economic analysis demonstrate that ruxolitinib cream represents a cost-effective use of NHS resources in adults and adolescents >12 years of age with non-segmental vitiligo with facial involvement who had received prior TCS/TCI. Comparisons against NB-UVB with or without TCS demonstrated that ruxolitinib 1.5% cream is a dominant treatment option associated with lower costs and greater HRQoL benefit over a patient's lifetime. In comparison with no active treatment followed by NB-UVB or not, ruxolitinib 1.5% cream is cost-effective at the WTP thresholds accepted by NICE.

4.2 Strengths and Limitations

Results for the comparison versus NB-UVB (with or without TCS) were robust and any uncertainties arising from the assumptions underpinning the ITC, or the uncertainty associated with the remaining model inputs, are not expected to change the overall conclusions. Despite the limitations of the ITC that informed the cost-effectiveness analysis, ruxolitinib cream is less costly and more effective than NB-UVB irrespective of the variability in the RPS/F-VASI comparative efficacy inputs.

Findings of the comparison versus no active treatment (either followed by NB-UVB or not) showed that several clinical inputs are pivotal for demonstrating cost-effectiveness, with the discontinuation/dropout rate in the post-treatment phase of the maintenance health state for ruxolitinib cream, the risk of relapse after ruxolitinib treatment, the probability of F-VASI90 initial response to ruxolitinib cream and the probability of no regain response input in the optional retreatment phase for ruxolitinib cream being particularly influential. The same inputs for no active treatment are also among the influential model inputs, bearing in mind that discontinuation/dropout rate and no regain response inputs for no active treatment are conservatively based on ruxolitinib data due to lack of relevant estimates from the TRuE-V or the LTE studies. In addition, the probability of F-VASI response with no active treatment is assumed to be constant from week 24 to week 52, which is another conservative assumption likely to underestimate the cost-effectiveness of ruxolitinib cream.

The CEM structure has been revised to closely reflect the TRuE-V and LTE studies while incorporating the design and data from the HI-Light study to allow comparison of all relevant treatments suggested in the ACD. To account for heterogeneity in trial designs and paucity of long-term effectiveness data, assumptions related to the durability of the treatment effect and efficacy of retreatment with each treatment option were necessary but should be accounted for in the decision-making process.

4.3 Conclusion

The decision problem considered in this cost-effectiveness analysis considers positioning of ruxolitinib cream as the 2L treatment option for patients with non-segmental vitiligo who have not responded to TCS or TCI alone, or for whom TCS or TCI are contraindicated, not tolerated or otherwise medically inadvisable. The model structure has been revised to ensure consistency with the NHS clinical practice, to align with the committee preferences and address comments in the ACD, and to reflect pivotal clinical data accurately. Results indicate that ruxolitinib 1.5% cream, compared to current treatment options, represents a cost-effective use of NHS resources in the target population.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ruxolitinib for treating non-segmental vitiligo in people 12 years and older [ID3998]

Appendix B: Clinical inputs

March 2024

File name	Version	Contains confidential information	Date
ID3998 Ruxolitinib for vitiligo_Appendix B_redacted	**1.0**	**No**	28th March 2024

Appendix B: Clinical inputs

A.1. Clinical Inputs

The clinical inputs file embedded above presents all clinical data used in the cost-effectiveness model for both the base-case and scenario analyses. It includes pooled baseline characteristics, clinical efficacy data which inform model transitions, and adverse event data.

NICE National Institute for Health and Care Excellence

Ruxolitinib for treating non-segmental vitiligo in people 12 years and over [ID3998]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 21 February 2024. Please submit via NICE Docs.

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

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NICE National Institute for Health and Care Excellence

Ruxolitinib for treating non-segmental vitiligo in people 12 years and over [ID3998]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 21 February 2024. Please submit via NICE Docs.

Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Incyte Bioscience UK £25,000 The company has co-funded (with another pharmaceutical company) a project which the Vitiligo Society is managing, aimed at raising of vitiligo and the recent research our charity has conducted. The research highlighted the challenges of those living with vitiligo, and the work seeks to rise public understanding of the condition and awareness of our support services. The funding was received in 2023, and the project work will continue until May 2024
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	The recommendation not to approve this treatment for use in the NHS leaves people living with vitiligo without any available effective treatment for the condition. Our research shows that people with medium to dark skin are more likely to have the quality of life severely affected by their vitiligo, and by preventing access to this treatment, this group are put at a greater disadvantage.

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NICE National Institute for Health and Care Excellence

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2	We have concerns due to the number of people that are contacting us within to purchase this treatment privately, due to its currently lack of availability via the NHS. By continuing to prevent people from accessing this treatment on the NHS those from lower social economic background will be preventing from accessing one of the few effective treatment options for vitiligo. Furthermore, we understand from feedback via our support groups that those in more public facing jobs such as hospitality, retail, teaching and care etc will often experience a great social impact from their vitiligo. These roles are often linked lower salaries and lower social economic status.
3	We are concerned that an overwhelming majority of our community [redacted] expressed a shared desire for more effective treatments or a cure for vitiligo, and this recommendation will be a devastating decision for people living and struggling with their vitiligo. It will make our community feel that their condition is not important, that the social and psychological impact they are feeling is not valid.
4	We are concerned that with [redacted] of our community reporting that vitiligo has a negative impact on their mental health, that this result will exacerbate the impact. Many people are holding on for more treatment options, and this recommendation will send a clear to our community that even if treatments are developed, they may not be grant access to them. It will take hope away from people who are already emotionally very vulnerable.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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

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

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NICE National Institute for Health and Care Excellence

Ruxolitinib for treating non-segmental vitiligo in people 12 years and over [ID3998]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 21 February 2024. Please submit via NICE Docs.

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Name	[redacted]
Organisation	Vitiligo Support UK
Comments on the DG:	

Are the recommendations sound and a suitable basis for guidance to the NHS?

"We are the patient support charity, Vitiligo Support UK. Our CEO has worked with patients for over fourteen years, and has vitiligo herself. Thus, we bring a lot of experience of the condition and have also worked on various Guidelines and patient information leaflets relating to the disease and the current treatment modalities.
As a patient support group, we have responded in detail at each stage of this appraisal process and provided two patient experts for the committee meeting. Comments from our members are provided here in this submission as well, which we trust you will take seriously and find as moving as we have done, in people's descriptions of the impact of vitiligo on them or their family member.

We have the following further points to make, as we consider the decision not to approve use of ruxolitinib in the NHS to be incorrect, based on untenable proposals and, indeed, inequitable.

1. Vitiligo is an auto-immune disease with concomitant comorbidities, including, in particular but not limited to, thyroid disease. Whilst it does not involve lesions, exudate, physical symptoms, "flares" in the disease, the question of suffering and its "degree" in relation to vitiligo appears to us to be a philosophical one rather than one of the clinical measurement of how people with vitiligo suffer and whether that is genuine or not, because it is not "physical" in those terms.
In following that path, i.e., you don't have pain or itch or exudate, so your condition can't be worth treating, this inevitably implies that those (many) conditions like vitiligo that cause profound psychological distress, social anxiety, reduce participation in external activities and family life, and create a pressure to conform to "normality" requiring one to "camouflage" your disease from others should be dismissed or diminished. There is a significant prevalence of these attitudes in relation to vitiligo and we are concerned that this has supported the environment that permitted this decision.
Our skin disease is a disease. For decades, we have had no treatment for our condition because it can be dismissed by those who do not have it. For decades, we have been treated as an apologist amongst other skin diseases, and the treatments that we are offered are only minimally effective and belong to the aetiology of other skin diseases. Ruxolitinib is the treatment that vitiligo patients have been waiting for. It is a first-in-kind treatment and it actually targets the cellular action that cause our disease. Please can you review your decision on the basis that we have long awaited acknowledgement of the severity of our disease and its impact; on the basis that this treatment is the equivalent step in treatment to the use of

biologics in psoriasis and we deserve this investment into our treatment; and finally, that failure to acknowledge this need means a failure to acknowledge the seriousness of this autoimmune disease and allows the subsequent diseases that may develop to also be ignored, at the cost of patients' physical health and wellbeing.

2. It is not our role to enter into the debate as to where in the treatment pathway ruxolitinib properly belongs, as this belongs to health economists, to the NICE committee and to the company. However, if phototherapy is to be treated as the comparative treatment for this new topical JAK inhibitor, we ask that you listen carefully to the patients' experiences we have provided of trying to gain access to this treatment. If a patient was to seek phototherapy treatment, then, first of all, the patient would have to persuade their GP to refer them to secondary care and dermatology. The waiting lists for dermatology are very long, and patients are triaged within the waiting list so that urgent "inflammatory" conditions are seen as a priority (in addition, 2WW causes further issues within waiting lists, of course, absolutely rightly).

This means that a vitiligo patient would probably need to wait for the maximum time quoted on the My Planned Care website. This preliminary appointment would require the patient to advocate again for their referral to phototherapy ("inflammatory" conditions that achieve results quickly using narrowband uvb are prioritised). At all stages, the patient must be an informed advocate for their care, pitching their case to be allowed to the next stage. This is difficult for many people, and after a first refusal from the GP, frequently couched in inappropriate language, they may well give up. These patients are not shown in the figures for hospital coding or accounting, because these are people who have desperately sought an effective treatment for their vitiligo but who have been overwhelmed by the need to present their case consistently and persistently. This also discriminates against those without the skills and confidence to build and present a case for their own treatment.

Following referral, the patient must then commit themself to attending for up to a year. The hospital may be close by; however, it is more likely to be at a distance. Parking is very difficult and expensive. Public transport is erratic and indirect. The patient must manage family responsibilities, work responsibilities, the demands of education and then the general strictures that apply to a course of treatment. Phototherapy is not a course of treatment that is accessible, simple, controllable or low-cost. We understand the health economics of pitching an existing treatment against the new alternative. However, please understand more fully that accessing phototherapy is increasingly becoming a pipe dream rather than a reality for vitiligo patients. Comparing a topical treatment like ruxolitinib that can be used in the home to one that requires such an arduous journey psychologically and physically to attain is not appropriate. Again, we urge you to consider this as a novel treatment for our disease, one that will revolutionise, in terms of practicalities and disease-appropriateness, the treatment of vitiligo.

We are not alone in believing that this is the first real effective treatment for vitiligo, as a patient support group that advocates constantly to help people navigate the current NHS treatments for vitiligo. This treatment has been

approved for home use in the United States. This treatment has been approved for home use in the European Union. Recently, France took a further step and, since 31 January 2024, have approved it for prescription by a hospital-based or private dermatologist within France and 100% reimbursed by the state. We believe the reason that this novel treatment has gained approval across the world is because it provides, for the very first time in many decades, access for patients to a targeted treatment that will bring positive effects in terms of repigmentation and concomitant improvement in psychological welfare, while also reducing demand for scarce hospital-based treatments such as phototherapy.

3. The landscape of skin diseases has changed, and we believe that the decision made by NICE does not adequately recognise that at this point in time, changes in appearance as the result of a quixotic and progressive disease have a more significant impact than the date in which most clinical decisions appear to be founded. Modern life is completely different from ten years ago. This means that a disease that causes you to look different changes fundamentally the way in which you can interact with this modern world. That is not as a result of vanity, not a trivial response to life, or only for those who are engaged in social media; physical difference is even less well-tolerated than ever before. As vitiligo patients, there is no route to manage that experience. There are very few psychodermatology services available to dermatology patients in England and Wales. There are almost no general psychological services provided that acknowledge or can manage the distress and anxiety that appearance change brings with it. Most importantly, people with psoriasis and atopic dermatitis have unique clinical tools to manage their conditions: specific treatments approved for them to tackle at root the disease that manifests on their skin.

Vitiligo patients must also manage the frequently bruising experience of talking about their disease with healthcare professionals and must live with treatments that very rarely bring about repigmentation. There is nothing available that can significantly help patients manage this disease currently within the NHS. This is why ruxolitinib is so important. It is a treatment that fills in those massive longstanding gaps in the treatment pathway. Ruxolitinib is a treatment that offers control, management, and a specific reduction in the cellular pathway that causes depigmentation. Psoriasis and atopic dermatitis have these treatments. They were approved by NICE considering the evidence of these patients' experience of disease and the clinical efficacy of the treatment. We ask that you reconsider the decision not to approve this clinically efficacious treatment for our condition. We suffer as all patients with skin diseases suffer. We have waited a long time for research to bring a treatment for our skin disease. Please treat vitiligo in the same way as other skin diseases have been treated, here and in Europe and provide this treatment for vitiligo patients.

4. Reference is made to the clinical trial and to its flaws, specifically in relation to the use of a vehicle cream as the control group within the trial. This was a trial lead by world experts in vitiligo, designed to prepare a solution to the disease that could be used globally. We can critique the inclusion and exclusion criteria, the means of statistical analysis and the use of a vehicle rather than a comparison with an active control substance, perhaps suggesting that the UK's predominant topical treatment should

have been used. This strikes us as an insular approach. In addition, the evidence has been sufficiently clear and sufficiently rigorously obtained to convince the Food and Drug Administration in the United States and the European Medicines Agency in Europe to clear it for topical use in vitiligo. What makes the patients here different? What makes the drug different in England and Wales? Is it simply cost? So, when you, NICE, examine the equations that would permit you to approve this treatment, do you weigh in the student at university unable to enjoy his life there because he has vitiligo on his face, and cannot access treatment? Do you weigh in the woman who avoids contact with her extended family because she has vitiligo everywhere on her body, and she has been dismissed at every stage of seeking treatment, in the end being offered only a bleaching agent for her few remaining patches of unaffected skin? Do you factor the impact on all the children facing adolescence in our TikTok, Instagram, Reddit world? Or the new means of meeting your partner across age groups, that depends on apps and the provision of an image, rather than meeting at work/church/the water cooler. This new society will not go away. Do you understand the importance your appearance pays in all social transactions? People's vitiligo will never go away. Unless you make the decision to recognise its impact, unless you make the decision to treat it as a skin disease like psoriasis, worthy of a treatment that is a global first, worthy of being treated. We ask you to add to the equation the very real suffering of vitiligo patients in this country, dismissed by doctors, diminished by your decision, a snapshot of which is provided here in the comments. We have waited for this treatment for decades. Please make it happen for us."

General Comments

"I am a patient with vitiligo. I want an easy treatment that is for my specific skin condition, and ruxolitinib represents this. I have tried phototherapy and other treatments but had to discontinue due to the ongoing cost and time impact on my life. A topical treatment is something that I could easily use. If you believe that phototherapy is a viable treatment option for vitiligo, then I suggest you talk to some patients who have tried to get access to it, to patients who have given up due to burns, or because the treatment causes higher pigmentation on surrounding normal skin. It is not a targeted treatment and you can only normally treat the whole body rather than small areas of skin as you can with this topical treatment."

"This treatment brought hope to many patients like me who struggled to access even basic creams in primary care. We've faced dismissal, being told that treatments, including phototherapy, don't work. Thus, we were thrilled at the prospect of accessing this brand-new treatment that works properly for vitiligo and allows for treatment breaks and subsequent effectiveness. Contrast this with phototherapy, which is often a struggle to access and has alarming risks such as skin cancer and aging. If given the choice, I'd choose this effective topical treatment. Since that's not an option, I implore NICE to choose for us, allowing us to treat our skin condition at home with real results."

"For years, since the 1950's my Mother, Grandfather and Uncle and myself have searched for and tried all medications thought to have some effect on restoring pigmentation in Vitiligo including UVB therapy. I have visited a variety of dermatologists all to no avail, mostly, I fear, through lack of interest and knowledge on the part of GP's and dermatologists, apathy even. I receive expensive creams and ointments every month that do NOT work costing the NHS but I apply them in hope.

"It is shocking and deplorable that I am now denied any hope of access to the one innovative treatment namely Opzelura/Ruxolitinib known to have excellent results for people with visible vitiligo. Yes, this treatment may be expensive but has proven efficacy unlike and compare to the several expensive creams issued to me every month by my GP mostly in vain. "

"Assumptions are made that vitiligo is 'just' a skin disorder that can hardly be detrimental to health. Think again. My Grandfather, my Uncle, my Mother and now myself have been shattered by this visible skin disorder that leave us open to ridicule, stares, jibes and critique as though we were monsters. This has never been more true than now, in a culture where looking beautiful or perfect or even normal have became the norm of being socially accepted. The effect on mental health mostly due to antisocial behaviour of others makes us reclusive, withdrawn and to some extent living in the shadows of shame and self disgust."

"We see hope with this topical treatment that prevents waste of application of large amounts of useless creams or dangerous UVB therapies and then strip it way, what gives you that right? Please make it possible for us to get the one treatment so long in the making so that we can once more hold our heads up high."

"This treatment is first-in-class and therefore no real comparator exists. You compare to phototherapy which has a significant cost for patients which must have an impact on the figures. To add, phototherapy is not a practical solution for most with limited access due to distance to travel and work commitments. So, does this mean that for vitiligo, no new drug will ever be approved? What if that were the case for psoriasis and the approval of expensive first-in-class treatments for it which are now used routinely in clinical care. Do not treat vitiligo as a poor relation, we suffer extensively from the impact of our disease, both physically & mentally. Please listen to our appeal."

"I am a vitiligo patient and I've learned about ruxolitinib from Vitiligo Support UK.

I first noticed it in 2016, and it very quickly spread throughout my body and face. It has made big impact on my self esteem, and it's upsetting having to explain to people what it is and that it's not contagious. Can you imagine how desperate I am to be offered a treatment specifically for vitiligo.

"When I first heard about Ruxolitinib, I was excited.

It was given approval in Europe, then MHRA approval and I had high hopes that, because it was so innovative and so effective compared to all existing treatments, I would be able to use it within the NHS. I am very disappointed to hear that NICE believes that phototherapy is a more cost effective treatment and dismisses this treatment.

Phototherapy treatment is not convenient. Can you imagine what it is like as a patient, going out in all weathers to the nearest (not very near) phototherapy unit, parking if you can, attending, then having to get to work and apologise again for being late. I myself am a full time carer for my mum and cannot afford the time to travel for these treatments. Why should we? when we could use this unique and effective treatment as part of our getting-ready-for-work/day routine and be treating it as we go about our day to day life.

I understand the issue of costs, but I also know that over the years since the beginning of the NHS, as a skin condition we as vitiligo patients have never had a treatment approved for our specific condition. Is it not time that some money from budgets was finally found for our vitiligo? Being dismissed by a dermatologist and being told that there is no cure and that I have to learn to live with it is heartbreaking. We need to be taken seriously, as it is having a big impact on our mental state. Please please have some compassion for us and approve Ruxolitinib."

"This treatment is first-in-class, and there is no real comparative treatment as we have nothing! NICE are comparing it to phototherapy, which carries significant costs and time demands for patients, inevitably affecting the figures as these are not shown. Does this mean that no new drug will ever be approved for vitiligo? Imagine if that were the case for psoriasis or eczema and the approval of the expensive first-in-class treatments for them, which are now routinely used in clinical care for them. Please do not treat vitiligo as a lesser condition. We suffer extensively from the impact of our disease; we need a treatment specifically for this disease."

"I am a patient with vitiligo. I have followed the progress of JAK inhibitors from the beginning in the US, to this current topical treatment. I understand that NICE are considering this from the viewpoint of cost effectiveness. In this, NICE is comparing it to phototherapy. It strikes me that illustrates a key accounting point, which is the importance of accounting for invisible costs

that still have an impact on healthcare decisions for the patient, the most important individual in this process and, indeed, the one who through their taxes funds the NHS. Comparing the cost of ruxolitinib to the patient (one visit to secondary care; one follow-up via teledermatology; one local visit to fill prescription) to the costs to the patient of phototherapy (one visit to consultant for referral; visit to phototherapy unit in secondary care for MED; multiple visits to phototherapy unit across a twelve month period involving time away from work/education, ancillary costs, impact on skin of initial erythema), it is clear which treatment provides an economically more cost effective option to the patient. Please may our costs and time be factored into this decision?”

“NICE's decision seems to suggest that vitiligo isn't as important as similar skin conditions like eczema and psoriasis, which have approved treatments funded by the NHS. But ruxolitinib targets vitiligo specifically, unlike what's currently available, and rejecting it just keeps us sidelined."

“As a person with vitiligo, I've experimented with various treatments like topical creams (which weren't tailored for my condition and proved ineffective), and I've also undergone phototherapy (prior to the current waiting lists). However, phototherapy is quite burdensome. It requires strict adherence to a year-long treatment schedule, longer than many other skin conditions. While it may result in pigment restoration initially, relapses are common due to the challenging nature of treating vitiligo. Furthermore, access issues often arise, either preventing further phototherapy sessions or due to reaching the maximum allowable treatments. In contrast, this unique topical treatment offers the advantage of reuse in case of relapse, eliminating access barriers associated with phototherapy. It represents a significantly superior, more effective, and more convenient option for vitiligo treatment compared to previous methods, including phototherapy.”

“This treatment is new and there’s nothing else like it. They’re comparing it to phototherapy, which is expensive and hard to get. Does that mean that we will never get a treatment for vitiligo? Other conditions such as psoriasis got new and expensive treatments, so why not us? Please listen to us and give us a chance.”

“As a sufferer of Vitiligo I can not emphasize enough what the approval of Ruxolitinib would mean to us. We deserve our own treatment for this illness”

"I have had Vitiligo for almost 20 years. Different creams which were prescribed did not make any improvement. I did hear about the light phototherapy at my local hospital. This would involve 2-3 visits per week and over a 6 month period, not practical for most people. This new treatment which I believe was developed in the USA under the Guidance of

Dr John Harris called (ruxolitinib) has undergone extensive trials and been approved in the USA and the European Union.
So at last a treatment which surely is the best option for all Vitiligo sufferers. This new treatment which has excellent results and can be used at home must be the way forward.
NICE do the right thing and really help people like myself to get back skin pigmentation."

“You compare phototherapy with this treatment, which seems reasonable, except that where I live, access to phototherapy is really hard. Many people live considerable distances from hospitals, especially if they don't live in major towns or cities, making accessing phototherapy arduous. Frequent attendance at regular intervals also poses challenges, as does managing work and personal obligations around treatment. Contrast this with treating a specific area at home, a process unbelievable to most vitiligo patients, but offered to us with ruxolitinib. We really need this simple effective treatment.”

“I have Vitiligo and the only advice I have had when asking for treatment is that any treatments have a side effects that may cause skin cancer, I have never been offered any phototherapy or anything else, my Vitiligo affects me a lot as it is very noticeable. I implore NICE to choose for us, allowing us to treat our skin condition at home with real results. And enable us to not have people staring at us and be able to enjoy being outside without worrying where the next patch will appear.”

“I am commenting on behalf of my 12 year old daughter who was diagnosed aged 10, this condition has had huge implications on her confidence and self esteem, despite our best efforts to reassure her. What is heartbreaking in this day and age is to tell her there is no cure, and I don’t know why. This condition effects so much more than skin, and when our young people are struggling so much already with mental health since lockdown, so much more needs to be and can be done to help ease the debilitating impact of vitiligo which is so much deeper than skin alone.”

"As someone who has struggled with vitiligo for years, I am all too familiar with the emotional toll this condition can take. The pigment loss on my skin has progressively gotten larger and more visible, making me self-conscious. I often feel anxious and depressed about my appearance. The current treatments are unfortunately not suitable for me.”

“This new treatment provides real hope to patients like myself. I sincerely urge the committee to recommend NHS funding for this vitiligo treatment so it can start benefiting patients without further delay. It has the potential to greatly improve quality of life for those with vitiligo for whom current

therapies have failed. I eagerly await access to this promising medication myself."

"As a 28 year old female with vitiligo, I've followed the development of JAK inhibitors from their inception in the US to this current topical treatment. I understand NICE is considering this from a cost-effectiveness standpoint, primarily comparing it to phototherapy. However, this highlights a crucial accounting point: the importance of factoring in invisible costs that still impact healthcare decisions for the patient. When comparing the cost of ruxolitinib to the patient (one visit to secondary care, one follow-up via the phone or Zoom, one local visit to get the prescription) to the costs of phototherapy (a visit to a consultant for referral, a visit to a phototherapy unit in secondary care for MED, multiple visits to a phototherapy unit across a year involving time away from work/education, other costs), it's evident which treatment provides a more economically cost-effective option to the patient. Please consider factoring in our costs and time into this decision. I also have not been offered phototherapy via NHS despite having rapidly spreading vitiligo for 4 years.
More needs done to support and help vitiligo suffers. Vitiligo has impacted every aspect of my life: work, friendships, relationships, my self esteem and confidence, the clothes I wear, how to cover up. I absolutely hate the skin I live in and would do anything to change it. Please consider helping us suffers with vitiligo see the light."

“When I was told there was no treatment and no cure for my vitiligo 20+ years ago my anxiety went through the roof and depression set in. Doctors and dermatologist were extremely rude, brushing it off as ‘cosmetic’. When you feel like you have no control for how much it could spread or how fast, makes your mind race. It really feels unfair that this condition is deemed ‘something you have to learn to live with’.

“My daughter was diagnosed with Vitiligo in October 21 when she was 8 years old. She is affected by it considerably, her confidence and her fear of people noticing and or commenting. She worries about being in the sun and her skin tanning, further highlighting her vitiligo. Although we have had various creams prescribed nothing has worked, everytime there is hope that something will make a difference but it never does. The dermatologist who confirmed her diagnosis of vitiligo offered minimal support and just advised us to apply suncream. It has an enormous impact on her life at such a young age.”

“I'm really disappointed that NICE doesn't think our skin problem is as important as other ones like eczema and psoriasis. They've approved treatments for those, but not for us. Ruxolitinib targets our skin issue specifically, so I hope that NICE will think again. It is almost impossible to get access to phototherapy, and we as patients have been forced to treat

our skin disease at our cost. We have never had a specific treatment for our skin disease. Now, we really need NICE to approve this one for us..... Having this topical treatment is priceless for us sufferers.... Please reconsider. [redacted]"

"I have been suffering with Vitiligo for 4 years now and it has a bearing on everything I now do with my life. I have spent in excess of £5000 per year to manage it using protopic creams, specialised sprays from a London dermatologist and my own UVB lamp. Even with all these interventions, it still does not hamper the spread. People who do not suffer from this autoimmune disease cannot understand the stress and anxiety it causes which impacts every aspect of your life. I implore you to reconsider your initial decision and allow the people who need this treatment, to be able to access it readily, to provide some form hope that we are able to get back control our bodies and hopefully lessen the stress on our minds."

"I am a vitiligo patient, and I've heard about ruxolitinib from Vitiligo Support UK. When I first heard about it, I was desperate due to the impact of vitiligo. I waited eagerly, hoping that, because of its innovation and effectiveness, it would become available through the NHS. I'm deeply disappointed that NICE deems phototherapy a more cost-effective treatment and dismisses this breakthrough treatment. Imagine what it's like, having to trek to the nearest phototherapy unit in all weather conditions, dealing with parking challenges, and then rushing off again. Now, imagine being able to use this unique and effective treatment as part of your daily routine, treating your condition as you go about your day. I understand cost concerns, but I also know that vitiligo patients have long been neglected in terms of treatment options. Isn't it time some funding was allocated to address our needs?"

"I was diagnosed with vitiligo aged 12 and have tried two rounds of phototherapy treatment with no success. I have had a few years of dormant vitiligo but the awful thing about the condition is that it can spread quickly without warning. Last summer it suddenly appeared across half of my face leaving me extremely self conscious of my appearance but also terrified that the skin on my face would burn leaving me no choice but to spend my own money on suitable sun protection. As far as treatment I was spending an hour commuting to a hospital three times a week for several weeks (at great expense) for treatment, which did nothing but leave my vitiligo more pronounced. I would urge NICE to look beyond the cosmetic issues of vitiligo and see the psychological impact that having such a visible condition can cause."

"NICE's decision implies that vitiligo is less deserving of treatment compared to similar chronic skin conditions like atopic dermatitis and psoriasis. However, these conditions have licensed medicines approved by NICE for routine NHS commissioning, highlighting a disparity in treatment

options. Ruxolitinib offers targeted treatment for vitiligo's underlying processes, unlike existing options, and its rejection perpetuates the neglect of our condition.
I have been living with vitiligo for the last 8 years and I have been struggling with the emotional impact of this condition. This medication would change my life and the life of thousand people ."

“I have had vitiligo since 2008. It is a daily mental battle and has had a significant impact on my mental health. Access to treatment in the UK has not been easy, with many visits to different GPs and Dermatologists who don’t seem to appreciate this is just not a cosmetic condition, but one which has severe impacts on people’s lives. This treatment has been approved in other countries and has enabled significant improvement to those with vitiligo. I am longing for the day that this treatment is available so that I can improve my mental health and start living my life without having to battle the day emotional distress I have with my vitiligo.”

“I’ve had vitiligo for 5 years, healthcare professionals are dismissive saying that there isn’t a ‘cure’ and we just need to live with it. Having olive skin means it plagues my life on a daily basis, I mainly have vitiligo on my hands, arms and face and I feel incredibly self conscious and because of the stares and comments I regularly find myself withdrawing from professional and social situations, the effect this condition has on people’s mental health cannot be underestimated, it’s a real and serious issue and must be addressed. This treatment is brand-new and there's nothing else like it. NICE are comparing it to phototherapy, which is expensive and very hard to get access to. Does that mean we'll never get a new treatment for vitiligo? Other conditions like psoriasis get new treatments, so why not for vitiligo that has a very similar impact of the suffers lives. NICE need to listen to us and give us a chance and help change the lives of thousands of people.”

“My son has had vitiligo since he was 8 years old. He is now 17 and at stage in his life where he should be wearing clothes of his choice, holidaying with friends and generally having a life where he is not stared at and made to feel different. Instead he keeps covered up and makes excuses not to go on holiday, as he knows he would have to wear fewer or shorter garments and draw attention to himself. I’m not sure if Nice have truly considered the psychological effect this condition has on people. Surely the cost of a cream outweighs the detrimental effect this condition has on mental health.”

“My vitiligo began at a very young age and spread over an extended period of time until it covered about 80% of my skin. Unless you have experienced this kind of change in your appearance it is hard to imagine how psychologically devastating it was, especially as a child and then a young

adult. Every doctor I saw was dismissive of the condition and said there was no treatment. So I hid my skin for decades, becoming a virtual recluse. My vitiligo dominated my thoughts and impacted negatively on virtually every aspect of my life. I lost my self confidence and even my sense of identity. But the worst thing was the lack of any hope that a treatment would ever become available in my lifetime. There were even times when I felt life was not worth living. Finally, after decades I was offered some phototherapy which I was told by another discouraging doctor might or might not help. But this meant travelling to another town three times a week over an extended period of time, which was not very feasible whilst working. I strongly believe that if a dedicated vitiligo treatment were available on the NHS, GPs and dermatologists would by default adopt a more constructive attitude with their vitiligo patients. And, above all, those patients would have some real hope of improvement."

"I have had vitiligo for 34 years, since turning 19, and have lived a relatively solitary life because of it. I can only wonder how my life would have turned out if a cream like this was available when I was young, as it could now be for people who are developing vitiligo in 2024. For the past three decades all suggested treatments by indifferent dermatologists have been ineffective and time consuming. The prospect of a successful treatment now must be pursued in order for young people to fulfil their potential and not become recluses, like so many sufferers have in the past."

"I've had vitiligo for many years, and when I first learned about this treatment, it gave me hope for the first time. I believed, like in European countries, we would gain access to it and conveniently treat our vitiligo at home. I am deeply disappointed that this isn't the case. What distinguishes a vitiligo patient in France from me? Must we still be treated as inferior in the realm of skin diseases?"

"I have had vitiligo for a number of years. When growing up I didn't know what it was and can remember feeling such shame that I would attempt to scrub it away in the bath with a scrubbing brush. As I have got older I still feel paralysed by the embarrassment and hide parts of my body away where I have vitiligo. To know that there are treatments out there that are effectively unavailable to me is awful. It's difficult to put unto words the mental strain and stress that Vitiligo has put upon me over the years. There is still a large amount of stigma associated with vitiligo through ignorance. The thought that youngsters will be starting their own Vitiligo journeys andexperiencing the same feeling that I have held for years, even though there are possible treatments available, doesn't feel quite right. I implore those responsible to make treatment widely accessible and available for those in the UK."

“I have had vitiligo for 3 years and it has spread exponentially during this time. My dad has had it for almost 50 years too. I have tried topical steroid and protopic as directed by my dermatologist but to no effect. Being quite an "outdoorsy" person, being told to stay inside out of the sun on high UV days was devastating. It makes you feel excluded from everyday activities most others can enjoy. It's time for something else.”

“My daughter had had vitiligo since she was 10 and it had been very difficult for us to deal with this condition. The anguish due to uncertainty and having few treatment options. Although we live in Oxford there are no nearby Phototherapy centres nearby that we could attend without having an enormous effect on my daughter's life education. Hence, we did not pursue Phototherapy. Having the option to use a convenient medication would have been enormously beneficial for out daughter.”

“My daughter was diagnosed with Vitiligo just before her 10th birthday. This has had massive impact on her confidance and social life. She lives in constant fear of spreading. Where our county NHS doesn’t even own Woodslamp to diagnose we had to travel miles away and pay for diagnosis. There is no phototherapy option near by either without travelling 30 miles. This treatment gives that hope. Where tackling Mental health is NHS biggest priority, patients with visible condition like Vitiligo which has huge psychological impact not only on the individual suffering but their whole family is treated so lightly. Why?”

“This treatment brought hope to many patients like me who had battled to get access even to creams in primary care. We have been so rebuffed, dismissed by being told that treatments, including phototherapy, don't work, that we were thrilled when we thought that like other countries we would soon have access to this brand-new treatment that does really work for vitiligo, and that allows you to take a break from treatment, then go back and for it to work again. Imagine trying this with phototherapy where it is a battle to get access in the first place, and you are limited in your lifetime to the number of courses that you can have. It also has high risks in relation to skin cancer and skin aging. This topical cream does not have those side effects. If I was allowed to choose, I'd choose this effective topical treatment. I don't have that luxury so I ask NICE to choose for me and allow me, like other skin disease patients, to treat my skin condition effectively and cost-effectively at home.”

“My daughter was diagnosed with vitiligo at the age of 10, she is now 13 and has extensive white patches, this puts an enormous strain on her on a daily basis not only physically but emotionally. She has tried protropic cream which was prescribed by a private dermatologist. I hope that this medication will be approved to offer hope to so many that are desperately affected by this.”

“As a dad of a 13 year old daughter who has vitiligo, watching her daily battles with this is awful. Hearing about this new medication brought hope to us as a family that she would get some treatment she so desperately would like. We understand that the cost is a implication but no price should ever be put on a person's wellbeing.”

"I was diagnosed with vitiligo at 45 within 2 years it had ravaged a large part of my body, I class myself as lucky as being offered phototherapy so make the hour long round trip for seconds of therapy in the vain hope it will by some miracle give me my pigment back, stop me constantly feeling self conscious, not dread summer, feel stupid when both the 2 NHS. Trusts I’ve been treated by make me feel vain as I have “fair skin” and “other people with darker skin” have it worse…
The psychological impact is something the medical profession can’t measure but having a single treatment recognised for vitiligo would help not those suffering today but the generation to come, please given us hope"]

“I have only recently been diagnosed with Vitiligo as a 36 year old woman and have found the attitude and dismissal of health professional astonishing! The attitude is “learn to live with it” which is not helpful. There is no treatment available to help me with this condition and this should be changed! It has a huge effect on people’s mental health as well as physical effects and an option of treatment would save lots of people.”

"I have vitiligo since I was 8 years old, back then it was just my finger tips, under my arms and my thighs, i don’t ever remember being diagnosed with it, I am now in my 50’s, and my body is now covered in Vitiligo I have never been offered treatment apart from the advice to stay out of the sun and keep covered up.
Growing up I remember I always looked different to everyone else and had daily battles being looked at, even being told not to scratch my sunburn as that’s what someone else thought it was.
Through the years I have become ignorant to what other people think, if treatments were available in my early days I would of moved heaven and earth to access them"

“Vitiligo is serious illness and having this treatment is critical to help people suffering from it…Vitiligo materially reduces life quality and causes psychological damage…after a long time without any solution sufferers deserve access to this.”

“My 9 year daughter has vitiligo. It covers much of her neck and her face and is extremely noticeable, even with fair skin. It is starting to affect her

confidence, the clothes she will wear, the style she will wear her hair in. When new children meet her it is almost the first thing they comment on. At only 9 her mental health is suffering and I worry daily about how much harder this will be for her as she progresses through her teens. The chance to have access to a drug which would hopefully ease the visibility of her condition would mean everything. [redacted]"

"My daughter has vitiligo, aged 9. She faces adolescence with vitiligo on her face, amidst a teenage world obsessed with appearance, and this makes me both worried and sad. We were given a steroid cream to try on her face, which I was anxious about because of the side effects. Then we were swapped to Protopic. Then all treatment was stopped for her, which I find very hard to understand. She is young so is at an age to respond well to treatment and is also in a place with her age where treatment is really vital to help support her psychologically as well as physically. This cream would absolutely be a change in our world and would help her regain pigment on her face in time for teenage years. Please reconsider this decision, as my daughter is relying on you to treat her skin condition like other skin conditions and make a positive decision for her and all other patients."

"I'm a mother to a newly diagnosed 8 year old with vitiligo. In the space of less then a year a small white patch on her neck has developed into multiple sizes of white patches all over her body. It has been a tough journey so far. She is dealing with what seems daily changes to her skin, other people questioning "why" and "what"....she hates it. She is only 8 years old. This journey will be one she'll deal with throughout her life as she grows up. If there is a treatment available so that she and so many others with vitiligo might not have to experience the emotional and psychological distress associated with vitiligo they should be given a chance to access this treatment."

"My wife has had vitiligo for over twenty years; no useful treatment has ever been offered by her doctors. Now there is finally the chance of a treatment that could actually do some good. I don't understand how NICE can reject this, given there are no effective or easily available alternatives."

"My daughter was diagnosed with vitiligo aged 8, she is now 36. Only treatment offered was steroid cream and camouflage, neither of which was successful. Any treatment easily used and accessible is extremely welcome. Although not painful itself vitiligo can have a devastating effect on those who have it, especially younger people. I urge you to approve this treatment which would mean so much to many."

"I have had vitiligo for 14 years and it has given me low self esteem and anxiety, it seriously effects your mental health it's not just a visual thing.Any

treatment or help is only a good thing and I hope it gets approved. Every patch takes more of the person I use to be , I hope people realise it's not just a physical visual thing .”

“My partner has suffered with vitiligo for many years, mainly on her face. With olive skin, it’s quite pronounced. It affects her confidence immensely and affects everything we do…where we holiday, where we sit for shade, socialising has almost halted as she’s lost all self esteem! She became self employed so she didn’t have to see as many people!! Protopic didn’t work; phototherapy had some success but was short lived before the pigment was lost again after burning and as a self employed business owner, so much time and money was lost travelling to the hospital. She has been clinging on to this hope of this new topical miracle to get her life back. She won’t be allowed the oral medication that may come in a few years due to cancer history so this is cream is her hope. Please, please approve this.”

"My daughter has suffered vitiligo manly in her face for most of her adult life. It has really affected her life and confidence. Treatments offered to date have had little or no success.
The news that this new treatments was coming filled us with hope. It will be devastating to people like my daughter if this hope is taken away."

"I developed vitiligo while going through the menopause, this was 10 years ago.
It came on virtually overnight & 30% of my body was affected. Prior to this I had never heard of Vitiligo.
It developed slowly after that & I am currently 40% affected.
My confidence was severely knocked & it affected holidays, clothes & social events.
A cure would be amazing."

“I first developed Vitiligo at the end of 2015 just before a new job which caused me a great deal of anxiety as a key part of the role was meeting new people and developing relationships with donors. As someone with brown skin, I was very concerned about how it would look. I avoided visiting my family for months and stopped wearing short sleeves or shorts and avoided visiting hot places. I was offered phototherapy but could only go to the hospital twice a week rather than the recommended three. I did this for months and some colour came back but once I reached the maximum limit and had to stop treatment the vitiligo continued to expand. I have tried numerous tans and camouflage creams and I currently spend a considerable amount of time covering up my patches and being anxious about the colour coming off on my clothes - I don't wear smart shirts anymore unless the colour will not show on the collars. I also have Type II Diabetes and sleep apnea and the added pressure of dealing with Vitiligo makes me depressed at times and has caused psychological stress which

has impacted my personal relationships, including my marriage which ended after 16.5 years, and the my career choices. I am desperate for an effective treatment that will restore my confidence and help me achieve more in life."

"It has been extremely difficult for my child to get effective treatment for her vitiligo over the last two years. We have seen several NHS Drs who have provided protopic creams to no avail. This new treatment would be transformative for children like mine who suffer from mental and emotional distress. This is a revolutionary treatment for vitiligo and the slow slog of phototherapy available which isn't always available and doesn't work very well anyway could be avoided. The treatments available right now are not efficient enough."

"I developed vitiligo prior to my abdominal sarcoma cancer diagnosis. It started on my legs but now covers all of my body. I have become paranoid about developing skin cancer and my mental health has been adversely affected to the point that when it's sunny I won't go out incase my skin burns. There seems to be nothing out there to stop these patches developing and they now cover all of my body. I have to cover up to prevent being stared at and to be honest? It's so underplayed by GPS it's as if it's just something I have to live with. But it's disfiguring and so depressing to be stared at 24/7 that I feel very isolated. A cure would be amazing and would give me one less thing to worry about among the increasing list ."

"I was diagnosed with vitiligo following the birth of my son. I was suffering from PPD and PPA and the diagnosis was awful. It was the pandemic and I was told I would not be able to see a dermatologist because it was "a cosmetic condition". My family could see I was suffering and sent me money so that I could pay to see a private dermatologist who offered me topical creams. That felt like a bit of hope for me which I needed to hang in there. I felt lucky at the time because it is incredibly difficult to even get any treatment at all due to the dismissive attitude of doctors (both GPs and consultants). The creams have not helped my vitiligo of course because there is no single *available* treatment specifically for vitiligo. The impact of this disease has been deep and immense for me. It has affected every corner of my life. I developed quite bad anxiety and went into a deep depression as it spread. I lost so much confidence. Mostly, I felt hopeless because I was told repeatedly by doctors it was a cosmetic condition- but daily I feel HORRIBLE. My skin itches unbearably as patches a spreading. It keeps me awake at night. Every time a new patch forms or spreads I go into another depression because every time I feel I'm getting used to my skin again it changes. I try not to look in mirrors some days. My skin is forever changing and I am learning to live with it but I struggle to understand how there is so little understanding and support for all of us who are struggling and suffering through this. As human beings we deserve to have the same dignity and respect and compassion that others have when they

receive a medical diagnosis- and if there is a treatment out there to have full and equal access to it- not to be told repeatedly that our disease is a cosmetic one, while holding some hope just out of our reach."

"My son 16 has been recently been diagnosed, he is trying to come to terms with changes in his appearance whilst navigating gcses. None of the creams available from nhs have made any difference to his condition. This is so important to make available as it has such an impact on mental health."

"My son has developed vitiligo over the past couple of years and none of the creams or treatments that have been prescribed so far have had any significant impact. Any new medicines that come onto the market should be granted in the UK so to at least give people who suffer from vitiligo a chance to reduce the impact of this condition."

"I first notice patches of vitiligo in 2018 whilst on holiday in Florida. When I came home I visited a GP who told me there was nothing that could be done, looking for a second opinion I paid to visit a private dermatologist. This appointment was a disaster in which I was told to be grateful I was white skinned and told again there was nothing that could be done.

I visited a different GP a year later and asked to be prescribed Protopic, the GP reluctantly did this, I tried it for a period of 6 months but had no improvement and hated the side effects.

I would welcome the opportunity to try a new treatment as my skin condition has made me feel hugely self conscious and affected my confidence especially in summer when I can no longer cover up."

"I have suffered with vitiligo since my youth and I am now retired. As a dark skinned gentleman, it has always been very prominent on my face and hands. I would have been very grateful for a treatment like Ruxolitinib to have been made available to me over the years. I would have been even more grateful to be able to offer a promising treatment like this to my patients in practice who would come to me, desperate for a solution to their vitiligo. The mental health impact of this skin condition should not be under estimated."

"I was s extremely disappointed in the decision NICE made not to approve the use of ruxolitnib within the NHS.

I presented with Vitiligo in 1970 at the age of 9yrs.
Over the years the condition had worsened. I have never been referred to a dermatologist as various GP's have been very dismissive of the

condition....even as far as saying " it won't kill you , learn to live with it"! Obviously I have 'lived' with it....my Vitiligo has continued to spread over my face, axilla,chest, waist, genitalia....I have never psychologically adjusted to this condition , I have paid for private pigmentation tattooing of my areola when my local NHS Trust refused to pay for it.
On a personal level I have avoided close relationships because I loathe my body with Vitiligo.

Considering cost-effectiveness, NICE compares ruxolitinib to phototherapy, overlooking hidden costs like time away from work and personal commitments associated with phototherapy. Ruxolitinib's simpler treatment regimen and reduced impact on patients' daily lives make it a more economically viable option. Additionally, being a first-in-class treatment, ruxolitinib lacks a direct comparator, challenging NICE's assessment methodology."

"After suffering from Vitiligo for the past 30 plus years, I was so incredibly disappointed that NICE have not approved the use of Ruxolitnib in the NHS. Vitiligo has affected many areas of my body, most extensively, my face, hands and chest. I am extremely self conscious and hate the stares during the summer months. It's a constant battle to avoid getting burnt in the sun as the consequences of this skin damage could result in life threatening cancers. This condition is often dismissed as just something we need to just 'get on with' but its impact on physical and mental health cannot be underestimated. To have the opportunity of a non-invasive and effective treatment available on the NHS would be life changing for so many and I just don't understand the methodology surrounding NICE's decision in this case."

"I have suffered with vitiligo since I was 34, I have just turned 70 and life has been miserable and stressful. Doctors generally dismiss patients with comments such as 'learn to live with it' OR 'be thankful it's not cancer' This is not helpful or kind. My worst nightmare is that my daughters or grandchildren will develop vitiligo so we need a cure NOW. I'd like to think that vitiligo would be taken as seriously as psoriasis and eczema"

"I myself don't have vitiligo but both my ex partner and my son have got it. I have at first hand see how difficult it can be having this skin condition that has no cure. It takes a huge mental toal with patches spreading and every spring the sun comes out it and the skin gets the tinies bit of sun new patches appears and the struggles it brings especially when it appears oon the face. It's not something you can get used to since it's also contantly changing. Hard to enjoy the sunshine when the patched either burns quickly or stick out even more because the unaffected skin gets darker. Most doctors have very little knowledge about this condition and we were just told. "get used to it there is no cure". People with this condition really needs

to get the this medication and the hope that there might be a posibillity that something could work."

"I have had vitiligo for 10.years, it came on overnight and I was 50% covered within 3 months. I am mixed race with dark coloured skin so the vitiligo is more visible on myself than it may be on others.
It was a very stressful few years coming to terms with my changing appearance and I still get stares and comments to this day. All previous treatments I have tried have been unsuccessful and this new treatment would bring hope to myself and others who suffer with this condition. It can greatly affect a person's confidence and cause them to become depressed and anxious about venturing into the outside world. This new treatment would be a god send to so many of us."

"I have had vitiligo for 9 years which appeared after to giving birth to my first son. Over the years it has got worse and worse leading me to dress differently to how I used to in order to cover it up. I also now dread the summer! Getting in a swimsuit fills me with anxiety when all I want to do is have fun in a pool with my 3 little boys without being so self conscious. I've tried various "treatments" which of course did not work. Something like this would literally change my life!! As well as many others."

"I have had vitiligo since my early 20s, over the last couple of years it's knocked my confidence and patches started to appear on my face. When I first noticed it I refused to go out for 3 days with my young kids at the time. Even to this day I hate going out especially in the spring/ summer.
Unless you suffer with vitiligo you have no idea how we all feel having to deal with it. My husband doesn't understand my paranoia about it, and it's very frustrating.
So please think of how we feel before you just reject something you feel "isn't going to work" or not worth "the money" etc - think of us who have it and our mental health. This could make us sufferers feel better within ourselves"

"I was shocked and worried when I noticed this skin discolouration creeping across my shoulders and begin to creep up my neck and chin and has currently stopped there. I was diagnosed with Vitiligo approximately 4 years ago and am anxious about its progression. I have noticed changes when exposed to minimal sun and am fearful of further change. Anything to help with this disease would change the lives of me and countless other people and children. Please help"

"I have had vitiligo for around 7 years now after developing it during pregnancy with my third child. It had a huge psychological impact on me and treatments I was offered made no difference. I am fair skinned so was

advised that phototherapy was not advisable because of the risk of burning and developing skin cancer. I have had to change the way I dress and alter my hobbies and time spent outside to protect my skin. I cannot enjoy time outside or holidays with my children as I used to and that does take its toll. I am luckier than others in that mine is not as visually noticeable but for those where it is it has wide reaching social impacts. A treatment like this would make such a difference to me and to many others lives."

"I was diagnosed with vitiligo when I was 12, my later school years were very very difficult. By the age of 18 the use of PUVA and steroid cream helped with re-pigmentation on my face, meaning my confidence at university and early 20s was increased. Around age 27 my vitiligo returned with steroid creams no longer having an improvement, by this time I was in a position where I was more prepared to deal with my health change and mentally more able to deal with my changing face. Whilst I still find it very difficult (make up to cover, SPF everyday) I do believe that not having visible vitiligo on my face in my 20s has helped me in being able to start my career, being confident enough to go out and meet who are my life-long friends and my husband.

PUVA and steroids do not work for everyone and so if this treatment was another option then there will be more chance to reduce the impact that vitiligo has on so many lives, hopefully facilitating young people to have the best start in their adult life that they can."

"This treatment would be life changing for anyone with Vitiligo like me who feel self conscious of their body to the point where they no longer do the activities they love or even go out of the house without makeup. I don't think the psychological aspect of this disease can be underestimated and the prospect of treatment has given so many people hope."

"I was diagnosed with vitiligo 20years ago and since then I have lost almost 99 percent of my pigment. Over the years I have tried every treatment available but unfortunately without success. This condition really knocks your confidence and self esteem and more focus should be aimed at providing solutions that may work for different people. Any new treatment would make a huge difference to people who have vitiligo."

"I have had vitiligo for over 10 years and it still affects my confidence everyday. I have tried various treatments and any new ones would be most welcome."

"I was diagnosed with vitiligo about 10 years ago. At the time it was a few spots on my hands, nothing to concern myself with. The doctor almost dismissed it, I have never been offered any kind of treatment. Since then it's

steadily spread and in the past couple of years has spread onto my face. The facial discolouring I really struggle with especially as I have olive skin. The difference medication could make would be amazing and would change people's lives."

"I have had vitiligo for over 50 years...its everywhere. No treatment ever offered. It's appalling, no other condition, which affects me mentally as well as physically, would be ignored in such an off hand manner.
Please please let suffers try any possible options...any medication or creams could make a huge difference for so many. This condition seems to get worse not better and is causing distress for so many. I have had to learn to cover up and put up with it but it still causes me embarrassment and upset. Really not acceptable."

"I have had Vitiligo for 3 years. Every single day I have to look at myself in the mirror and I see it getting worse and worse.

I work in sales and my appearance unfortunately hinders my earning potential. I am a man so wearing cover up is not an option.

I wouldn't wish this on anyone. Please help."

"I was diagnosed with vitiligo a few years ago at the age 37. As an adult it was a shock to see my physical appearance suddenly start changing so rapidly. I have been self conscious about wearing clothes that showed my patches, but now it is really starting on my face it's something I can no longer hide.
It's hard enough to learn to deal with this as an adult woman, but it would be even harder to deal with it as a young person, or as a man who may not want to resort to makeup (which doesn't cover well anyway!)

Please don't underestimate the huge impact Vitilgo has on people's mental well being. Please help."

"I have been diagnosed with vitiligo when I was 24 years old. This was shocking , depressing and upsetting. I wouldn't leave home for a week , crying , thinking of a suicide. I thought I will never get married, because my skin was starting look patchy. I was worried that if I have children than they will inherit this too. I have tried various treatments , one of them included UVB sessions. I travelled 2 times a week to NHS hospital , which was 30-45 minutes away . I had just under 200 sessions with a very slow repigmentation process. Now, 5 years later all gained pigmentation has gone. There is no effective treatment at the moment , creams , uvb are all waste of time and NHS funds. So if rixolitinib is the only solution at the moment, then please let patients to have it. Living with a vitiligo is not a life."

"I have suffered with vitiligo for over 12 years and receiving my diagnosis was devastating. It is extremely difficult to accept and live with this awful condition because of its nature: it spreads, inexorably, causing panic and profound distress. Current treatments are inconvenient, time-consuming, and offer little hope: a few spots of new pigment perhaps, that we hope will miraculously join up and restore our skin to what it was. They don't.
Give us hope again. Let us live in sunshine again. Make this proven treatment Ruxolitinib available on the NHS, and restore the skin and lives of countless people. You could need it too."

“I developed vitiligo at 36 years of age. I am now 42. I find it very difficult to deal with. It is slowly robbing me of my identity and causes me a great degree of unhappiness in my own skin. It stops me from doing the things I used to enjoy and some days I just want to hide away from the world and cry. I know there are other possible treatments such as light therapy but this is extremely time consuming and inconvenient for me with work and 3 young children. I also know that such treatment is very hit and miss in achieving good results and even if you retain some pigment, it is likely to return at a later date. The current creams on offer are also hopeless. It would mean the world to me to have access to a new cream to try which is convenient and has been shown to give better results than current available treatments. Please, please give us the chance to try it and hopefully regain some of our happiness and identity.”

“I've had vitiligo since I was 24, so nearly 9 years now. I have quite a few patches on my face and body, and my hands are near enough white now. I try covering my hands daily with fake tan but because of my job I have to wash/sanitise my hands a lot, so it doesn't last very long. I have to wear make up on my face even in the summer because I'm so self conscious about what I look like. I tried phototherapy and the closest clinic was about an hour away, plus I could only manage going once a week because I worked full time. I tried the usual creams prescribed (protopic) but they had little effect. After some time I got taken off the list for phototherapy because mine 'wasn't that bad'. Maybe not to someone else, but it is to me. I now have two young children so phototherapy would be even harder to try now anyway if I was given another chance. This medication would make a massive change to my life and mental health, as I feel vitiligo has robbed me of my identity.”

“I have had vitiligo since my mid 20s and mostly over my hands and body which I cover in the summer with fake tan. I have been to the doctors and never offered any form of treatment and no notice taken as to how it makes me feel other than ‘there’s no cure’. I am getting to the point where it’s noticeable and I have no path or options to take other than ‘just learn to live

with it'. More treatments should be made available if the options are out there"

"I began to see pale patches appear on my legs, hands and feet in my early 30s. Now in my 60s I have large patches of white all over my lower legs and my hands and feet. The appearance embarrasses me and I often wear long trousers in very hot weather rather than endure the stares and sometimes unwelcome comments from strangers. It has affected my confidence gradually despite my close friends saying that they don't even notice it. This cream can make peoples lives better. Suffering this condition may not have the profile of other high profile psychologically damaging medical or mental issues but I can assure you that there are people who have loss confidence over it."

"I've had vitiligo since I was 5. Now 40. I have extensive covering of vitiligo and I find it a daily struggle to have this condition. Some treatment would be really quite wonderful."

"As a person with vitiligo, I've experimented with various treatments like topical creams (which proved ineffective), and I've also undergone phototherapy. However, phototherapy is quite burdensome. It requires strict adherence to a year-long treatment schedule, longer than many other skin conditions. While it may result in pigment restoration initially, relapses are common due to the challenging nature of treating vitiligo. Furthermore, access issues often arise, either preventing further phototherapy sessions or due to reaching the maximum allowable treatments. In contrast, this unique topical treatment offers the advantage of reuse in case of relapse, eliminating access barriers associated with phototherapy. It represents a significantly superior, more effective, and more convenient option for vitiligo treatment compared to previous methods, including phototherapy."

"My vitiligo first started to show around 4 years ago but has spread rapidly. While I had no trouble in getting a referral to dermatology the treatment I have been offered has been limited to protopic and instructions on use and side effects have been unclear. I found the dermatologist dismissive, was advised there was no real treatment and that the best I could hope for was to slow the spread. I have not been offered any alternative treatment such as phototherapy and even if I had been I would be hesitant about possible side effects and the time commitment. It would make a real difference to those affected by vitiligo if there was an effective at home treatment available"

"I have Addisons which makes me have dark skin with Vitiligo as well you can imagine how awful it looks!! It's made me feel so self conscious and affects my daily activities with my family. Hate holidays when it should be

precious. We need treatment I did undergo. Phototherapy it burnt my patches. If there is any treatment we could try to make us feel better that's all we ask!! Fed up of people staring and feeling nervous when put and about."

"As a sufferer of Vitiligo for over 30 years I can not emphasize enough what the approval of Ruxolitinib would mean to me"

"My Vitiligo started when I was 19, When I got diagnosed I was offered no treatment and was told that nothing would work. I was told by my doctor to just get on with it and learn to love with it. I am now 33 and have watched it spread. I notice people staring at me, I notice people looking at my Vitiligo when taking to me. As a man make up isn't really an option. I do believe it has probably changed my personality to be more introverted. Scared to go on holiday or to get a tan as I know how much it will stand out. I have a young daughter and I am terrified that she may also end up suffering like myself. You cannot tell me that it wouldn't affect yours or anyone's mental health to have Vitiligo that's why I believe any form of treatment should be available to help people who suffer with Vitiligo. Ruxolitinib is proven to work so please make the right decision and make it available."

"I have had vitiligo for more than 20 years, mainly affecting my face which as you can imagine is probably the last place you would want to have this, as you can't hide it and it's the first thing that people will notice. I was just told there is nothing that can be done. It affects my confidence and mood and it's always been depressing to know there isn't anything that would help. I understand Phototherapy is an option but I've never been offered it. There is also the constant worry in the background that it will start getting worse and spreading. Any time I'm stressed, I stress more thinking about whether my patches will worsen. To have a convenient, at home treatment available would give hope to many of us affected. My 75 year old father is also affected over most of his body and it causes him a lot of distress. I know he would be overjoyed with a treatment being made available."

"I started with a small patch in my face during lockdown in 2020 and since then it's spread to almost 50% of my face. It's really affected my confidence being on my face it's constantly visible and the first thing people see. I'm petrified it will spread to my hairline and I could lose my pigment in my hair. Any new treatment would be amazing, all I've been offered was cream that did nothing to halt the spread or reduce the size of the areas. I really hope these comments help to get this approved."

"My family have suffered with Vitiligo for many generations, and now having had my own children, it is a real concern for me that they will also develop

the condition. And the fear that this will detrimentally impact their mental health and acceptance in a world that is already hard enough, and knowing that there a is medication that can help, but currently not accessible, it is heartwrenching as a parent. Reading all these other comments just reaffirms how necessary this medication is. So many suffering unnecessarily and exposing themselves to alternate dangers and barriers with phototherapy. Phototherapy is not the answer. And neither should Vitiligo sufferers be expected to just get on with it. The option to use this medication is there that has the ability to significantly improve sufferers way of life, and reduce wasted spend on other topical treatments that are known to be ineffective. We need to consider the environment, and surely the production of a product that actually works is far more beneficial than using multiple other products that do not make a significant difference, categorically.

Please help all sufferers of this scarring condition. It's impact is huge. We need to try something else. Very few conditions are you expected to just get on with it, and be told nothing can done. That is not OK!"

“Vitiligo has changed my whole life. I'm not the confident person I used to be and I'm suffering with depression on a large scale. I hate the person I am now”

“Vitiligo means I can not go out into the sunshine to enjoy my life. I have had to give up many of my favorite hobbies. I have lupus and I can not get phototherapy. None of the topical creams will work. If I can not get this treatment through the NHS, I will go overseas and get it. I am concerned that others will do the same and people will not be followed properly by their local GPs. Yes, please consider people with lupus and other conditions that prohibit phototherapy. In addition, the economic impact of Major Depressive Disorder is not considered alongside the financial cost of this treatment.”

“I started with vitiligo a couple of years ago after an extremely stressful event in my life. It rapidly spread and I felt so depressed and panicked. GP referral to specialist was over year wait. I was fortunate to be in position to pay for private consultation and then six months of light therapy which did help but was expensive, time consuming (2 visits a week) and left me sometimes quite burnt. I would have loved an easier treatment to access and for there to be something available to all who need it regardless of income.”

“My wonderful grandson now has this to deal with alongside studying hard for exam results he needs to follow the career on which he's set his heart. Surely if a treatment that actually provides some relief is produced it should be available given that the medications and treatments he has are so unsuccessful. The number of people living with vitiligo may not be as large

as some other conditions; but the strain both physical and mental is great. Please help!”

“I have had vitiligo for 10 years now and it has had such a big impact on my daily life. I wear make up on it at home as I hate seeing myself in the mirror with vitiligo visible. I never wash my face where my vitiligo is because I never want to uncover it to remember I have it. I carefully think of the placement and hair style I have for maximum coverage (make up helps but still often visible to me). I never wear my hair completely back as a result. Hot weather causes me to become nervous as my face becomes red when I’m hot and this makes the vitiligo more obvious. I would love a chance to try something that could actually help.”

“I have had vitiligo now for over 30 years. It makes me dread summertime and all the negative/insulting comments
I was given a course of phototherapy but no change. An at home treatment would be so beneficial”

“This condition is very hard to accept, you loose all your self confidence, it makes me feel very depressed anything that can help would change so many people’s lives”

“This condition deeply affects me. It started in my 30s. I’ve bought hand held lamps for narrowband uvb but not had any success. I’m trying black seed oil now. People with this condition need help and need treatment.”

"I had vitiligo since I was 3 years old on the face, after I was nearly 20 to 25 vitiligo spread to other parts of my body but in small patches especially in the waist part. also, my beard at vitiligo sites became white.
Vitiligo affects me a lot, especially in the part of Confidence.
During these years I did a lot of treatments like Tacrolimus and Calcipotriol Creams and also Phototherapy treatment.
All these treatments didn't solve my problem or if they did they did for a short period and the disease came back again
I wish one day we have that treatment that cures vitiligo totally without coming back.

[redacted]
Pharmacist"

“I've recently (last 2 weeks) been diagnosed with vitiligo (by gp not dermatologist as there is 4 years wating list on nhs, i cant go private as i don't have the money) noticed them 3/5 months back. and i've been

struggling with body dysmorphia since i was a teenager and I'm 32 now, so you can imagine how vitiligo has even made my body dysmorphia even worse I'm so so low! I'm constantly in distress, anxious and having panic attacks! I've been given protopic and the reviews on this is shockingly bad, I've only been advised to apply them on my patches 2 daily for 4 months and then go back to see gp! I cant afford uvb lights and all the expensive things to try and help the patches. When i came across ruxolitinib on the web and how affective it is and how it been approved in other parts of the world i found hope after 2 weeks of researching a looking for hope in finding how to help vitiligo! I'm soo soo disappointed that this cream is not been used to help us in the UK to treat vitiligo!"

"Not everything has been considered in this appraisal. Speaking as a lupus patient phototherapy is contraindicated for us. Additionally, topical steroids have been ineffective for me, and many other patients. Thus, ruxolitinib is the only treatment left for many patients.
The psychological impact of untreated vitiligo has not been take into account adequately. Vallerand et al (2019), people with vitiligo were at a 65% increased risk of major depressive disorder. While vitiligo does not increase the risk of skin cancer, it does result in difficulties being in sun. I personally limit sun exposure, wear SPF 100 when outside, wear clothing that is SPF protective, and yet I still burn and peel. This further socially isolates people with vitiligo, exacerbating mental health issues."

"Myself and son have been diagnosed about 7 years ago. My son was offered creams that did not work. My son has it really bad compared to myself on his body legs, especially his face. He has never been offered photo therapy even after asking. This condition makes us both very self conscious and our mental health is effected badly by this condition. Especially my son who is 17. Please find something to help."

"My mum has vitiligo, and I've seen it affect her over the years. She doesn't complain but I know that things like being outside in the summer, going swimming, wearing short sleeves all make her extremely uncomfortable. That's every summer, so you can see that the impact of vitiligo is significant. She also has it on her face so as you can imagine, she is very uncomfortable with this. She also, of course, worries about me and more so because she's tried treatments and they don't work. If this treatment was approved, I think it would make her day. I want her to be able to enjoy the summer again. I want something to be on offer, like it is for other skin diseases, that could help her treat her skin."

"My vitiligo makes my gender dysphoria as a non-binary person worse, as I do not feel adequately feminine. Covering it represents a substantial economic cost, and without it people with vitiligo are subject to discrimination."

“My son was diagnosed with segmental vitiligo to his neck/face when he was just 5 years old. Fortunately his vitiligo has not came hand in hand with any autoimmune diseases and he is a fit and well now 9 year old. For this reason his condition has been described as cosmetic. I would not describe a condition which affects mental health and increases risk of skin cancer as cosmetic. At a young age he accepted he needed to be smothered in suncream every day (as it’s not a place which can be covered) and we were fortunate in a way we were in lockdown so he didn’t need to face people while he (and us all) got our head around the condition. I am a mother who supports her child mental health and fights for support for him but to see him stand in the mirror after a week holiday, when his naturally tanned skin tanned even more, to breakdown and say ‘why is it so big now’ it’s breaks my heart that, in the eyes of medicine, his condition is cosmetic. We are fortunate to have a great dermatology department and they have offered Tacrolimus ointment but it did not work. Because of his age they are not willing to offer phototherapy just year. I have followed the trial of ruxolitinib and is excited about its prospects and fully support this consultation for its use in the UK. I know my son is too young for it just yet but I can only hope as he enters his teenage years this treatment will be readily available with proven success in the UK. It is about time Vitiligo is recognised as a disease which deserves treatment rather than just being labelled as ‘cosmetic’.”

"All three of our children now have vitiligo. Two had already been on long waits for treatments for over the last 5 years. The protopic cream the dermatologist gave our son made his skin so irritated he scratched himself at night till he was bleeding all over his back. After that experience we were much more cautious with our younger son who was not able to explain how it felt. We very much need better treatments and yes especially available to children, when the social and emotional impact can be especially great.

I also would appreciate dermatologists treating autoimmune skin conditions to be more supportive of patients wanting to try well researched whole health approaches. I found it incredibly frustrating how our dermatologists did not want to hear or support anything around vitamin supplementation when there is well documented research around vitamin D, B12, Zinc and Copper levels etc in Vitiligo. Our dermatologist was also dismissive of the impact of gut health despite incredible results in our son’s scalp condition after being on probiotics as well as some repigmentation of his vitiligo. I realise it is important for NICE guidelines to reflect the importance of this research in order for dermatologists to consider and support these options."

“My son is 9 and has was diagnosed with vitiligo 4 years ago. As a young boy he wasn’t hugely aware of it but at his age he is very conscious. We have tried tacrolimus without success. His vitiligo is on his neck/face and he has also started with a tuft in his hair. As parents we are desperately

supporting new treatments in the hope it never starts to affect his mental health."

"My vitiligo appeared at the age of 34 I am now 70 so more than half my life. I get really depressed about it and still very self conscious. Holidays in the sun are difficult but I go along for my friends and family's sake. My biggest fear is that my daughters or grandchildren somehow inherit it. Doctors don't seem to have empathy with comments like "just learn to live with it" AND be grateful it's not cancer"

"This new treatment gives vitiligo sufferers some hope and that at last it's being taken seriously. I have spent lots of money on treatments but nothing has worked so far."

NICE National Institute for Health and Care Excellence

Ruxolitinib for treating non-segmental vitiligo in people 12 years and over [ID3998]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 21 February 2024. Please submit via NICE Docs.

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

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None.
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We are disappointed with the provisional decision of the Committee not to recommend topical ruxolitinib within its marketing authorisation, although we acknowledge some concerns surrounding the economic model. It is important to remember that current, off-label, evidence-based treatments for vitiligo show only around 30%-40% success rate. Understandably, this fact leaves vitiligo patients extremely disappointed, disadvantaged and deprived of effective treatment options.

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	On the other hand, TRuE V1 and V2 trials were the largest trials on vitiligo so far, with robust outcome measures, which showed clinically meaningful response as well as response meaningful to patients.
2	We are concerned with the decision of the Committee not to recommend topical ruxolitinib. It is important to offer to patients with vitiligo, the most effective (as per clinical trials) and licensed treatment as soon as possible and preferably early on, to ensure that clinicians do not miss this "window" of opportunity to treat vitiligo early. As recommended in the BAD guideline (Eleftheriadou *et al.* 2022 10.1111/bjd.20596) for managing people with vitiligo, early treatment of vitiligo seems to be more efficacious compared with treatment of long-standing disease; therefore, there is an urgent need for an efficacious, topical treatment for vitiligo.
3	We are concerned that this recommendation may imply that people with vitiligo will be deprived of the effective topical treatment. There is no licensed treatment for vitiligo available on the NHS and results of currently available treatments on the NHS can often be unsatisfactory. There is an urgent need for an effective and licensed treatment for vitiligo patients in the UK.
4	This is the first ever treatment licensed for vitiligo. Currently, it is widely available in the USA and other European countries, whereas people with vitiligo in the UK are deprived of an effective treatment option for this psychologically devastating skin disease. Therefore, failure to make this treatment available through the NHS to people with vitiligo will increase the psychological distress they experience as a result of their condition.
	Section 3.4 and 3.7 We are concerned that the Committee believes that comparator for topical ruxolitinib should be whole-body hospital phototherapy. Whole-body phototherapy has a systemic effect on the body compared with topical treatments, which only act on the area of the skin on which they are applied; therefore, the choice of comparator (phototherapy) would be clinically inappropriate. There might be confusion of **whole-body** phototherapy (the traditional phototherapy treatment currently available across various hospitals in the UK) with hand-held phototherapy, i.e. phototherapy, which is applied to only one small area of the skin, i.e. **limited phototherapy** (as used in the Hi-Light trial). Although topical ruxolitinib could be compared with hand-held phototherapy, this latter is only offered in one hospital in England (Royal Wolverhampton NHS Trust); therefore, this comparison would not be reflective of current clinical practice.
5	Ruxolitinib cream is a topical preparation, which is marketed for application to a maximum of 10% of total body surface area; therefore, it would be appropriate to use it either alongside or following a trial of either topical corticosteroids or calcineurin inhibitors, rather than following (over) 100 hospital appointments for phototherapy.
6	We are concerned about the impression of the Committee that this innovative treatment option for vitiligo may be initiated by GPs in primary care. A global research study on the impact of vitiligo and perceptions of patients and healthcare professionals, reported that almost half of patients with vitiligo (44.9%) were initially misdiagnosed. Most patients obtained their diagnosis after 2.5 years (Hamzavi *et al.*) https://doi.org/10.1093/bjd/ljad245). Therefore, we believe that initiation of this treatment in secondary care with the possibility of shared-care agreement with primary care would

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	be more appropriate. It would also allow adequate monitoring, management of side effects and adherence to efficacy criteria (for all treatments for vitiligo) as established by the BAD guideline for the management of vitiligo (e.g. improvement in % of BSA affected after 3 months and decision on whether to continue treatment).

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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

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

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Name	[redacted]
Organisation	British Dermatological Nursing Group (BDNG)
Comments on the DG:	

Has all of the relevant evidence been taken into account?

"No as its very difficult for patients sometimes to attend phototherapy. This is due to cost of living, not being able to afford travel or carparking fees. Not everyone can take time off work.
Some hospitals dont have phototherapy departments or the service will be broken."

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I feel not as patients with Vitiligo are at risk of non melanoma skin cancers which in turn can result in more cost for the NHS. Cost can also be induced by the psychological impact - resulting in more time and resources for the NHS if these patients seek help.

Are the recommendations sound and a suitable basis for guidance to the NHS?

More treatment is required for these patients- they often have read about Ruxolitinib and the US evidence has been successful. Patients deserve treatment and hope they can have this on the NHS. It can be detrimental to patients self esteem when refused treatment. The evidence states already how many patients suffer from low self esteem and mental health issues. It is difficult for health care professionals to be so restricted in limited treatments

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

In skin of colour this is more common and they shouldn't be made to feel this treatment isnt available. There shouldnt be bias for a condition that is more common in skin of colour.

Name	Pawan Korpal
Role	Patient expert nominated by Vitiligo Support UK

Comments on the DG:

Has all of the relevant evidence been taken into account?
I submit that NICE should consider that it is not totally relevant or helpful to compare Ruxolitinib with off label treatments as one had proven effectiveness through specific trials whereas off liable treatments like protocol are hit and miss working for some and not for others. Ruxolitinib is a novel treatment and the first that is specifically for Vitiligo and effective.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
It is not totally reasonable to assess clinical and cost effectiveness between Ruxolitinib and off label treatments or phototherapy. It is expected that Ruxolitinib will be more effective clinically than off label treatments.

Are the recommendations sound and a suitable basis for guidance to the NHS?
Guidance should focus on the unmet need for an effective and proven medication for those with Vitiligo. Emphasis should be added that Europe and the US have approved this treatment.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
Vitiligo clearly impacts those of darker skin more significantly on a psychological basis. This ought to be considered

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	Viktoria Eleftheriadou

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	I am frustrated and disappointed with the provisional decision of the Committee not to recommend Ruxolitinib within its marketing authorisations. It is important to remember that currently available off label, evidence-based treatments for vitiligo show only around 30%-40% success rate. On the other hand, TRuE V1 and V2 trials were the largest trials on vitiligo so far, with robust outcome measures, which showed clinically meaningful response as well as response meaningful to patients. By not recommending Ruxolitinib for the management

Please return to: **NICE DOCS**

Ruxolitinib for treating non-segmental vitiligo in people 12 years and over [ID3998]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 21 February 2024. Please submit via NICE Docs.

	of vitiligo leaves patients extremely disadvantaged and deprived of this effective treatment option.
2	This is the first ever treatment licensed for vitiligo. This treatment is currently widely available in USA for almost 2 years now and other European countries, whereas people with vitiligo in the UK are deprived of an effective treatment option for this psychologically devastating skin disease.
3	Re Section 3.4 and 3.7 I am concerned that the Committee believes that comparator for Ruxolitinib should be whole-body hospital phototherapy. Whole body phototherapy has a systemic effect on the whole skin compared to topical preparations, which only act on the area of the skin they are applied to; therefore, the choice of comparator (phototherapy) would be clinically inappropriate. For example, it is like comparing a new spray for the throat with oral antibiotics. I believe that there might be is confusion of **whole-body** phototherapy (which is the traditional phototherapy treatment currently available across various hospitals in the UK) with the handheld phototherapy i.e. phototherapy, which is applied to only one small area of the skin i.e. **limited phototherapy** (as used in Hi-Light trial). Although theoretically topical cream such as Ruxolitinib could be compared with handheld phototherapy (hence for the economic model, information from the Hi-Light trial might be relevant); however, this comparator (handheld phototherapy is not reflective of clinical practice. Home handheld phototherapy is only offered by **one** hospital in England (Royal Wolverhampton NHS Trust).
4	Ruxolitinib cream is a topical preparation, which is marketed for application to a maximum of 10% of total body surface area; therefore, it would be appropriate to implement it either first line or following a trial of either topical corticosteroids or calcineurin inhibitors, rather than following (over) 100 hospital appointments for hospital-based phototherapy.
5	I am concerned about the impression of the Committee that this innovative treatment option for vitiligo may be initiated by GPs in primary care. A global research study on impact of vitiligo and perceptions of patients and healthcare professionals, reported that almost half of patients with vitiligo (44.9%) were initially misdiagnosed. Most patients obtained their diagnosis after 2.5 years (Hamzavi IH, Bibeau K, Grimes P, Harris JE, van Geel N, Parsad D, Tulpule M, Gardner J, Valle Y, Tlhong Matewa G, LaFiura C, Ren H, Ezzedine K. Exploring the natural and treatment history of vitiligo: perceptions of patients and healthcare professionals from the global VALIANT study. Br J Dermatol. 2023 Oct 25;189(5):569-577). I strongly believe that initiation of this treatment by secondary care with perhaps a possibility of shared care agreement would be more appropriate and would also allow adequate **monitoring and managing of side effects** and adherence to efficacy criteria (for all treatments for vitiligo) as established by the British Association of Dermatologists guidelines for the management of vitiligo (e.g. improvement in % of Body Surface Area affected after 3 months and decision to continue treatment or not). From my experience, Primary care physicians often refuse to prescribe topical steroids and calcineurin inhibitors to patients with vitiligo due to lack of experience, therefore I have concerns about Committee comments regarding initiation of treatment in Primary

NICE National Institute for Health and Care Excellence

Ruxolitinib for treating non-segmental vitiligo in people 12 years and over [ID3998]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 21 February 2024. Please submit via NICE Docs.

	care. I strongly believe that the treatment should be initiated by secondary care after a diagnosis of vitiligo has been confirmed by a Consultant Dermatologist. Following this, shared care agreement could perhaps be a way forward and would alleviate the burden of follow up appointments on the secondary care.
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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

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

Please return to: **NICE DOCS**

Single Technology Appraisal

Ruxolitinib for treating non-segmental vitiligo in people 12 years and over [ID3998]

Comments on the draft guidance received through the NICE website

Name	[redacted]
Comments on the DG:	

"I am a consultant dermatologist with 20 year experience in both teaching and district hospitals. I was a lead for a regional phototherapy service for a number of years and have treated many patients with vitiligo. This is my opinion and opinion of my patients that we need to make ruxolitinibe available to patients.
With best wishes

[redacted] Consultant Dermatologist"

Name	[redacted]
Comments on the DG:	

Has all of the relevant evidence been taken into account?

Yes

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

To a good extent

Are the recommendations sound and a suitable basis for guidance to the NHS?

Not sure

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Not on the above categories however it feels there is not proper empathy, and luck of understanding of the mental damage the people with vitiligo

experience because of the condition. So the cream will be a significant support

General comment

The statement Some people have phototherapy" disregards the challenges faced by vitiligo patients in accessing effective treatments. Phototherapy's inconvenience, it does not work in many cases, or is only effective in certain body parts, also combined with its limited accessibility, high cost and potential side effects, underscores the need for alternative options like ruxolitinib, which offers targeted treatment with fewer drawbacks."

Name	[redacted]
Comments on the DG:	

General comment

NICE's decision seems to suggest that vitiligo isn't as important as similar skin conditions like eczema and psoriasis, which have approved treatments funded by the NHS. But ruxolitinib targets vitiligo specifically, unlike what's currently available, and rejecting it just keeps us sidelined.

Name	[redacted]
Comments on the DG:	

General Comment

As a sufferer of vitiligo for 20 years and having followed the progess of medicine in this space I was really excited by the prospect of Ruxonitlib. To find that this may not be available on the NHS is extremely disappointing and I wanted to make this point to those responsible for the decision.

Name	[redacted]
Comments on the DG:	

Has all of the relevant evidence been taken into account?

"One of the problems that you have had is that there is no currently approved treatment for vitiligo, and hence you have no comparators for assessing the submitted product. Long-term use of a topical corticosteroid is not really appropriate because of side effects, especially if using a potent or highly potent topical steroid on the face. Topical corticosteroids are really only of any use in vitiligo of recent onset. Similarly, topical calcineurin inhibitors are only of limited benefit. Systemic corticosteroid treatment is very rarely appropriate in vitiligo, and should not be considered as a comparator. The problem about using any form of phototherapy as a

comparator is firstly one of general availability – narrow band UVB phototherapy is only available in certain centres and in those centres it is under extreme pressure so the likelihood of anyone with vitiligo getting a look in is quite reduced. Secondly generalised phototherapy is for generalised vitiligo, whereas the product in question has a license for use for vitiligo of the face. For facial vitiligo, a localised source of phototherapy, such as the Excimer laser or light source is an appropriate treatment, but this is only available in a very small number of centres in the UK. An additional issue, particularly with narrow band UVB is that after around three years post treatment quite a bit of any repigmentation that has been established will have been lost. Phototherapy cannot be used as a maintenance treatment because of the skin cancer risk. If your committee is looking for a comparators to the submitted clinical trial of ruxolitinib cream then I would propose that the most appropriate one would be a comparison of Excimer light or laser treatment for vitiligo of the facial area.

From [redacted]. I have extensive experience in treating and researching vitiligo over a period of greater than thirty years, and right up to the present day. I have no financial connection with the Marketing Authorisation Holder, Incyte. I am the patron of the Vitiligo Society, having [redacted]

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

From a health economics point of view, I would challenge your economists to assess the cost of a six month course of twice weekly narrowband UVB phototherapy. They will find that the cost will run to several thousand pounds. The cost of 20 treatments of Excimer localised phototherapy will be several hundred pounds.

Are the recommendations sound and a suitable basis for guidance to the NHS?

The objective of the treating physician is to arrange for his or her patient to receive a treatment with the highest likelihood of success at the earliest time after the onset of the disease. You will not perhaps have appreciated that vitiligo becomes more difficult treat with increased duration of established disease. In other words, treatment of recent onset patches is more successful than treatment of patches that have been presented for several years. Additionally, treatment in younger patients is more likely to be effective than in older patients and on this point, the Marketing Authorisation Holder's age point of 12 years and over is appropriate. Taking the entirety of my knowledge and experience of vitiligo into account, when I saw the initial reports of the effect of Janus Kinase-1 inhibitors on vitiligo, I was mightily encouraged, as I thought that at last, vitiligo patients have some hope. For decades now, vitiligo has been an orphan disease, Ruxolitinib cream is a treatment that we could offer to sufferer that would produce pigmentation in a reliable manner, being easy to administer way, with an acceptable side-

effect profile, without the necessity for expensive and frequent hospital attendance occasioned by phototherapy, that can be initiated at an early stage. Hence it is alarming to me that a committee composed of perhaps one could say a majority of individuals who may never have seen a patient with vitiligo or talked to them, has decided in the negative on ruxolitinib cream, a treatment to which we should be giving our full support.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

I do not really think your committee has properly taken into account is the severe psychological damage that vitiligo can have on the sufferer. You will find that almost all patients with vitiligo are severely affected from a psychological point of view. I believe you have underestimated the degree of this, and that the effect should enter your calculations to a greater degree than presently it does, especially in people of colour for whom the psychological damage is greater. I would challenge you to get further evidence from Professor Anthony Bewley of London or Professor Andrew Thompson of Cardiff University, on this subject.

Name	[redacted]

Comments on the DG:

Has all of the relevant evidence been taken into account?

One missing area of evidence is that of patient perspectives and expectations of treatment. Having an option prior to phototherapy that is not a steroid or calcineurin inhibitor may be significant especially for those patients who cannot attend phototherapy. Phototherapy is a prolonged treatment when applied to people with vitiligo and a large time commitment. Knowing how patients would feel about an alternative prior to this step in my opinion is very important.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The personal costs to patients have not been explored, especially in relation to willingness/fears around use of topical steroids/calcineurin inhibitors and commitment to phototherapy regimes. I appreciate this information may not be widely available, but it is very worth considering for further consultations.

Are the recommendations sound and a suitable basis for guidance to the NHS?

The requirement for comparison to phototherapy, although understandable, is not practical and will be difficult to determine on a holistic level for the patient. Although objectve scores for repigmentation/VASI would be available for comparison, there are several other factors to consider - phototherapy has a prolonged course (approx 50 treatments over 1 year) and involves a greater time commitment and patient burden when compared to a topical treatment.

Name	[redacted]
Comments on the DG:	

General Comment

I have had vitiligo for 10 years and it effects me mentally more than you can imagine, my vitiligo has never responded to the current steroid and topical treatments that have been available on the NHS and unfortunately for me it is constantly active and spreading, I am now 34 and it gets me so incredibly down that I have to cover up constantly because of the embarrasent of my skin, children often ask why I have white paint all over me, I understand they are only curious but the constant shame of the state my skin is in makes me really depressed and contributes hugely to my poor mental health

Name	[redacted]
Comments on the DG:	

General Comment

As a mother of a 16 year old girl I witness on a daily basis how impactful vitigo is on her quality of life. She does not live her life to the full because of this condition. As her mother it is heartbreaking to see this . We all want our children to live life to the full. For her without hope of new treatments her daily life is a battle. Even if she could only reverse the visible areas of depigmentation it would make a massive difference to the quality of her life. Please consider the impact this awful disease has on the life of people when making your decision.

Name	[redacted]
Comments on the DG:	

General Comment

"It is disappointing that this has been provisionally rejected. Particularly so as in France the cream has just been approved for use in their health system.

The stigma and impact of vitiligo should not be underestimated particularly in patients with darker skin types. Vitiligo patients have been historically neglected in the UK and it is a shame that this trend continues.

Whilst I appreciate the technical value of NICE's cost benefit analysis, in the dermatology clinic it leaves us with a practical problem: What will we tell patients who have failed phototherapy, who have tried protopic and topical steroids and who are desperate for treatment? Why should they be denied access to a treatment which has been shown to work.

Even if doctors and scientists appreciate the technical critique of ruxolitinib research and pricing, it will certainly be lost on
patients, many of whom have to deal with being stared at on public transport, stigmatised in their community and challenged as they try to form relationships.

I hope a more patient centred approach to decision making will be possible in the future which will take account of individuals experiences and stories about the effect of this problem on their quality of life."

Name	[redacted]
Comments on the DG:	

Has all of the relevant evidence been taken into account?

No because Vitiligo and the appearance of white patches on the face seriously affects the lives and mental health of those affected and as "Clinical trial evidence shows that ruxolitinib increases repigmentation and reduces how noticeable the vitiligo patches are" it should be made available to treat Vitiligo patients in order to improve their quality of life and mental health.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No because Vitiligo and the appearance of white patches on the face seriously affects the lives and mental health of those affected and as "Clinical trial evidence shows that ruxolitinib increases repigmentation and reduces how noticeable the vitiligo patches are" it should be made available to treat Vitiligo patients in order to improve their quality of life and mental health.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No because Vitiligo and the appearance of white patches on the face seriously affects the lives and mental health of those affected and as "Clinical trial evidence shows that ruxolitinib increases repigmentation and reduces how noticeable the vitiligo patches are" it should be made available to treat Vitiligo patients in order to improve their quality of life and mental health.

Name	[redacted]
Comments on the DG:	

Has all of the relevant evidence been taken into account?

"I do not think you have fully considered impact on people's mental health of vitiligo and lack of current treatment options.
Phototherapy is not widely available , is very time consuming and there is a limit to the amount of photo therapy a person can receive."

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

It is disappointing that decision seems to be a financial one , rather than clinical one.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I do not agree with recommendations that have been made not to recommend ruxolitinib. I do not think you have fully considered impact on people's mental health of vitiligo , ignorance they face from others and lack of other treatment options.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

I think the decision not to recommend ruxolitinib, indirectly discriminates against people of colour as vitiligo is more apparent in individuals with darker skin tones.

Name	[redacted]
Comments on the DG:	

General Comment

My nephew has been recently been diagnosed, he is trying to come to terms with difficult changes in his appearance while in important school year. None of the creams available from nhs have made any difference to his condition. This is so important to make available as it has such an impact on mental health.

Name	[redacted]
Comments on the DG:	
General Comment	

"I attended the consultation and was very disappointed that the company appeared to be so ill prepared and felt the frustrations from the NICE team.

The current treatment pathway isn't fit for practise, it is a postcode lottery and doesn't allow for those who have to work, if phototherapy is even offered in their area.

My consultant told me I am lucky that I am white. This is a very uneducated opinion and education should also be improved for health care professionals.

Living with vitiligo is a lifelong condition which effects every aspect of my life especially socially, professionally and personally. I avoid holidays, swimming with my children and even parts of my job have been effected as washing my hands would wash off my fake tan revealing my patches. My uniform doesn't cover my arms and I would be asked if i was contagious. Hours a week are spent covering patches, removing fake tan, re applying fake tan and wishing the sun to dissappear. Spontaneous plans are a thing of the past, incase my camoflage isnt in place. Vitiligo also effected my marriage.

Overall the physiological impact of this condition has been phenomenal for myself and I would like to think that if my children start to develop it there will be a successful treatment for them.

I would very much like to see the approval of this treatment, whilst it may be too late for some of us it's needed for the future vitiligo sufferes to improve their life."

Name	[redacted]
Comments on the DG:	
General Comment I have vitiligo for 8 years, I tried Pritopic Tacrolimus ointment for few years, it didn't work, then I went to the private hospital in Solihull for phototherapy for 20 times, it didn't work again, it costs a lot of money, the doctor asked me to try Dermovate ointment, it still didn't work, I felt hopeless and depressed, Ruxolitinib cream is coming into the market, that will give us hope, wish NICE take the second thought to approve this new vitiligo treatment.	

Name	[redacted]
Comments on the DG:	

General Comment

"Hello, I am a Consultant Dermatologist and the co-founder and lead of Skin of Colour Training UK https://www.soctuk.org/ which aims to provide excellence in training to dermatologists, GPs and other healthcare professionals in managing black and brown skin - a demographic disproportionately affected by the visible, and often detrimental differences, caused by vitiligo.

I regularly see patients with non-segmental vitiligo and saw 2 severe cases with extensive acrofacial and generalised vitiligo just last week in a locality that is not particularly diverse, with ethnicity mix in line with the national average for diversity.

Thanks for a thorough dissection of the evidence presented for making ruxolitinib for non-segmental vitiligo available on the NHS.

Many of the conclusions I agree with, but I do not get the sense that the impact of vitiligo on the Fitzpatrick skin types 4 -6 has been adequately taken into account by the EAG committee. Admittedly, the studies did not have an overwhelming number of these subjects included. Clinical study participation in the population most visibly affected by vitiligo is a complex issue couched in unethical and discriminatory research practices in the past.

My specific comments are given below in the hope that ruxolitinib, the 1st agent licensed for vitiligo, will be offered to all affected patients under the NHS umbrella."

Comment on section 1.1
Shame. This decision has been made on a health economics basis without, in my view, sufficient consideration of how acrofacial non-segmental vitiligo affects darker skin types. The UK population within this group are, for many reasons, often socioeconomically disadvantaged thus unable to procure this privately and often do not possess the skills or the means to advocate for themselves. Dermatology in secondary care has capacity constraints ranging from moderate to extremely severe. Thus, ruxolitinib's cost comparator, phototherapy is, at once, not a fair or viable option. Complementary therapies e.g. camouflage, are also beleaguered by limited access nationwide and unsatisfying efficacy.

Comment on section 1.2
"Despite comment above, I agree with this positioning purely on a cost basis. However, like tacrolimus, I hope that ruxolitinib (branded and/or generic) will soon be available in primary care.

Comparing ruxolitinib with phototherapy has its own challenges due to availability and the lack of robust, standardised evidence on its use in vitiligo."

Comment on section 3.2
The committee's recognition of the lack of licenced treatments for non-segmental vitiligo is noted.

Comment on section 3.3
Agree in light of its initial cost. In time, it is hoped ruxolitinib will be available in primary care.

Comment on section 3.5
The conclusion is sensible but seems unfair as the company will struggle to produce the evidence required to make a robust comparison with phototherapy and other topicals without commissioning prospective trials themselves, introducing further delay and driving up costs.

Comment on section 3.6
Fair conclusion.

Comment on section 3.7
As said before. A real comparison using current data with phototherapy will be extremely difficult, if not impossible.

Comment on section 3.8
Look forward to seeing how the company manages to revise their assumptions and any new data.

Comment on section 3.9
Looking forward to company data on patient-level BSA and dosing from their TRuE-V trials.

Comment on 3.11
Agree with committee's request for a revision on its assumptions regarding NHS Dermatology attendance to reflect expected clinical practice. I suspect, qualitatively, that the information will be in the company's favour as availability in the communities where people need it most is suboptimal.

Comment on 3.13 Adverse Events
Agree common adverse event cut-off should be revised downwards from 4% to 1%. Are there systemic side effects after a certain amount is used?

Comment on 3.13 Uncertainty in cost-effectiveness estimates and further analyses needed
True. Looking forward to updated information. Cost-effectiveness estimates with revised assumptions, representative of a typical NHS Dermatology clinic model, may give a QALY assessment in favour of ruxolitinib.

Comment on 3.15
Similar to the funding assessments made for biologic and immunomodulatory medications in dermatology (and other specialities) within NHS England, vitiligo's impact on the patient's QoL should be taken

into consideration as a means of balancing efficacy with stewarding resources.

Name	[redacted]
Comments on the DG:	

Has all of the relevant evidence been taken into account?

I would like to comment, I suffer from vitiligo and it has a big impact on my life. The treatments currently available in the U.K. are limited. The condition has a huge psychological effect on my life. This drug could change people life. It has been approved in other countries.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
I would like to comment, I suffer from vitiligo and it has a big impact on my life. The treatments currently available in the U.K. are limited. The condition has a huge psychological effect on my life. This drug could change people life. It has been approved in other countries.

Name	[redacted]
Comments on the DG:	

General Comment

"I have suffered with NSV for 40 years and can confirm that it has had and has a very distressing effect on my life. It has increased quite dramatically over the past few years.
I have been denied sunscreen on the NHS so it means total cover up. The face and hands are particularly problematical and I have suffered extreme sunburn on my hands.
It isn't viable to attend phototherapy sessions. For me, living on the Isles of Scilly, it would mean very expensive transport, NHS funded, and possibly not effective.
Ruxolitinib would be a life changing treatment and should be available for the sufferers of this devastating condition."

Name	[redacted]
Comments on the DG:	

General Comment

Vitiligo causes myself and my family such heartache. It causes extremely bad mental health issues. Children aged 12 and over will struggle endlessly with bullying due to the randomised attacks from this condition on a person's pigment.

Name	[redacted]
Comments on the DG:	
General Comment I am an individual who suddenly developed vitiligo 4 years ago. I have lost pigment in 70% of my face and hands and have numerous other large patches . The patches continue to appear. My confidence has significantly deteriorated. I notice people staring. Additionally, it is very difficult to manage sunburn. Even 5 minutes outside will result in burn. It is a logistical feat on hot days to manage hat, suncream, long sleeved clothes, shade. I would like to have the chance to have some pigment to prevent immediate burn, although I would of course continue to protect myself with cream and clothing. There is no alternative at the moment. Cover cream is time consuming to apply. Phototherapy is too time consuming as I work full time. Other topical creams do not work.	

Name	[redacted]
Comments on the DG:	
General Comment I along with others have lived all their lives having to cover their complete bodies and suffering with depression. This is the only treatment that works more than any other treatment. Please do not deny us the chance of hope in our lives . We have waited all our lives for this . Please see the importance of this hope to thousands of people and life changing	

Name	[redacted]
Comments on the DG:	
As a person who suffers from vitiligo on approximately 90% of my body any treatment would be better than nothing. I have not been offered phototherapy or anything else in the 15 years I have had this condition. If clinical trials have shown that this treatment does work I would be willing to try it as it would improve my appearance and therefore my mental health.	

Name	[redacted]
Comments on the DG:	
Has all of the relevant evidence been taken into account? [redacted] I have long and wide experience of managing severe vitiligo.	

This treatment is a major advance in the management of vitiligo. It is the first significantly effective topical treatment for vitiligo, with effectiveness similar to that of phototherapy.

Preliminary small studies of vitiligo combined with UVB phototherapy also suggest a synergistic effect with almost complete repigmentation in around 65-70% of patients (Pandya AG, et al. J Invest Dermatol. 2022 ;142:3352-3355).

It is clear that this is a major advance in the treatment of vitiligo. It is also clear that its place in treatment of severe facial vitiligo will be before phototherapy. So the cream will be prescribed and if it is not effective then phototherapy added in for combination therapy.

Facial Vitiligo is a very common disease, and the NHS has to be cautious about the cost implications of any new treatment for a common disease.

However, severe debilitating and handicapping vitiligo is a relatively rare disease.

I think the job of NICE is to differentiate the common mild vitiligo from the sort of devastatingly severe vitiligo which I have spent much of my career treating.

- At the mild end of the spectrum will be a white patient with a few patches of vitiligo in covered sites in whom the vitiligo is not striking unless the surrounding skin gets tanned in the summer.
- at the severe end of the spectrum will be a black African patient with severe involvement of the face . Such a patient may be unable to obtain employment as a result of the stigma of the disease, has a high chance of the vitiligo creating significant close relationship problems, may face social isolation as a result of the stigma. Such patients not infrequently suffer severe reactive depression with suicidal ideation. For certain groups, such as some communities from the Indian subcontinent with traditional marriage practices, severe vitiligo will often result in the person being considered 'unmarryable' in a community where the psychosocial price of this is devastating.

I think that the key here is to set criteria for disease severity so that Ruxolitinib cream is used clinically for the severe cases of facial vitiligo who need it. You will find that the number of patients and the expense to the NHS will be dramatically cut and become manageable if there is clarity about the severely affected patient groups who need this treatment as NHS treatment.

a) it is right that this should only be NHS prescribed by a Dermatologist with significant experience of treating vitiligo. I think there may be benefit in specifying this more precisely in terms of the amount of experience
b) define 'severe' vitiligo and then only approve it for that and not for milder cases. Define this using:

- measures of patient impact of the disease
- relevant quality of life measures
- patient's normal skin colour i.e. a measure of the colour contrast between the vitiligo patches and the surrounding normal facial skin
- percentage of facial skin surface with vitiligo.
- presence or absence of perioral and periocular vitiligo which are particularly socially disabling because of the key social role of these facial areas."

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
"No I do not agree with the Committee's comments on this.

Many of these severe patients will end up having Ruxolitinib cream in combination with phototherapy which will dramatically improve the current clinical outcomes from phototherapy.

The Committee seems unaware that many Dermatology Departments anyway currently have unmanageably long waiting lists for phototherapy, and frequently stop treating vitiligo with phototherapy completely as a result."

Are the recommendations sound and a suitable basis for guidance to the NHS?
No they are not. For those of us who have devoted our lives to these unfortunate patients the NICE Committee appears to have created a report which does not reflect the severity and importance of this clinical problem, and the lack of awareness of the importance of the new treatment to a relatively small group of severely affected patients is overlooked.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
This discriminates against black and Asian people on the basis of skin colour. Skin colour is the main determinant of the impact of vitiligo.

Name	[redacted]
Comments on the DG:	

Has all of the relevant evidence been taken into account?

"Impact on sufferers mental health not taken into account.
It is unforgivable that such a powerful and beneficial treatment should be left tantalisingly out of reach for Vitiligo sufferers."

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
No

Are the recommendations sound and a suitable basis for guidance to the NHS?
Poor access to cutting-edge treatments is one of the reasons successful skin condition treatments in this country continue to lag behind other rich nations

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
"Vitiligo is specifically difficult for people with black and brown skin. I am of African descent and the impact on my mental health and self esteem is so overwhelming it has at times, left me feeling suicidal.
I know from previous testimonies to the Vitiligo Group that others have felt the same."

General Comment
"I implore NICE to improve this product. It is crucial NHS patients with rare conditions get access to important new treatments.
I have suffered with Vitiligo since I was a teenager. I am now in my 60's. Over the years I have suffered stigma, embarrassment and discrimination. This has negatively affected my mental health and self-esteem.
Like most people with Vitiligo I have also suffered with feelings of self-consciousness, shame and isolation.

Denying me and other NHS patients access to this treatment will add to our suffering. The anguish caused cannot be underestimated.
Ruxolitinib offers hope to Vitiligo sufferers and the priority now must be to ensure all those who need it get access to this treatment as soon as possible."

Name	[redacted]
Comments on the DG:	

Has all of the relevant evidence been taken into account?
yes. My request is, can we please make it available to the private pharmacy where it can be purchased by paying actual cost. Please consider my request.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
Yes

Are the recommendations sound and a suitable basis for guidance to the NHS?
Yes

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
No

Name	[redacted]

Comments on the DG:

Has all of the relevant evidence been taken into account?
No, I feel NICE have not taken into account any evidence where patient voices are listened to. Have NICE taken into account any evidence where patient opinions about current Vitiligo treatment and cream are explores? Are there any studies of lived experience and has this research been reviewed?

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No. Recommendation seems to have been based on cost rather than clinical effectiveness of the cream.

Are the recommendations sound and a suitable basis for guidance to the NHS?
No. Care in the NHS should be person centred but the current recommendation suggests a blanket rule of not to prescribe the cream to all vitiligo patients rather than considering individual cases and the impact Vitiligo is having on a persons life.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
Has NICE considered the impact of Vitiligo on ethic minority groups? who often have darker skin tones, making Vitiligo more prominent. I feel the lack of consideration of this is discrimination on the grounds of race.

General Comment
The current recommendation from NICE regarding this cream is very disappointing. As a Vitiligo sufferer it is hugely disappointing that the cream is currently not recommended. It seems that your current recommendations are based cost rather than clinical effectiveness. Vitiligo is not just a cosmetic condition, it has a very negative impact on a person's mental

health and self esteem. The development of this cream brought hope to thousands of Vitiligo sufferers in the UK but this hope seems to have been dashed due to your negative recommendation. I am sure I am not alone in urging the committee to re-consider it's recommendation.

Ruxolitinib for treating non-segmental vitiligo in people 12 years and older [ID3998]

A Single Technology Appraisal

EAG appraisal of the company's response to the draft guidance

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Produced by

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1. INTRODUCTION

1.1. Background

On 11th January 2023, ruxolitinib for the treatment of non-segmental vitiligo in people 12 years and older was discussed by the National Institute for Health and Care Excellence (NICE) technology appraisal committee. This meeting led to the development of draft guidance (DG), in which the committee raised concerns about the evidence presented by the company for the clinical and cost effectiveness of ruxolitinib, and ruxolitinib was not recommended at this time. Specifically, the NICE committee raised the following uncertainties:

- The company did not present evidence comparing the clinical effectiveness of ruxolitinib with phototherapy (NB-UVB). The company reported that an indirect comparison with phototherapy was not feasible, however the committee considered that the company should provide comparative evidence for all relevant comparators, including NB-UVB.

- The company did not present full details and clinical effectiveness results for participants in the trials who had previously received treatment for their condition (the company's selected target population). The committee concluded that the company should submit a full submission of evidence for the prior therapy and target population subgroup that could be appraised by the External Assessment Group (EAG), including a comparison of ruxolitinib to relevant comparators.

- The patient access scheme (PAS) discount for ruxolitinib offered by the company and included in its economic analyses would only apply if ruxolitinib was prescribed in secondary care. However, clinical experts suggested that it would be preferable if ruxolitinib was prescribed in primary care, after a specialist diagnosis.

- The committee concluded that the use of vehicle cream as the comparator in the company's economic analysis was not appropriate and that the model should be amended to allow for comparison between ruxolitinib and NB-UVB. In general, there was uncertainty surrounding the appropriate comparators for ruxolitinib, including to what extent NB-UVB would be a comparator. The determination for the appropriate comparators to ruxolitinib would be informed by a decision on whether ruxolitinib would be prescribed in primary or secondary care, and evidence concerning the proportion of people eligible for ruxolitinib who would otherwise receive NB-UVB.

- The committee agreed with the EAG that there were flaws in the company's economic analysis that biased the results in favour of ruxolitinib and thus was not suitable for decision-making. They considered the analysis to not reflect the condition or the treatment pathway and that the following issues should be resolved:
    - The definition of treatment discontinuation did not reflect expected clinical practice and overestimated the number of people who would discontinue ruxolitinib by 24 weeks.
    - The analysis assumed that those in the non-response state after treatment with ruxolitinib would not experience any improvement in their condition, which the committee considered did not reflect that some people would receive another active treatment. The committee also considered that people should be able to transition from the non-response state if they experience an improvement in their condition and that the costs of the non-response state should not be capped at 10 years.
    - There was a structural error in that it was not possible for people who reached F-VASI 75 to 89 following treatment to transition to a maintenance health state, at which point they would stop treatment.
    - The model assumed that people receiving vehicle cream would receive re-treatment with vehicle cream if they subsequently relapsed, which did not reflect clinical practice. The committee also received advice that the proportion of people who were assumed to receive NB-UVB when in the non-response state was higher than expected by clinical experts, and that the company's assumptions surrounding the use of NB-UVB in the non-response state biased the results in favour of ruxolitinib. The committee concluded that the analysis should represent the treatment pathway that would occur in NHS clinical practice.
- There was uncertainty in the mean dose of ruxolitinib that would be used in practice, and assumptions around dosing had a large impact on the cost effectiveness of ruxolitinib. Data from the trial suggested that some participants used far in excess of the dose range specified in the marketing authorisation for ruxolitinib, which the company explained was due to a miscalculation. The committee concluded that the company

should present the individual patient-level body surface area and dosing data from the TRuE-V trials.

- The committee concluded that resource use assumptions for dermatology and psychological support used in the company's model were overestimated and biased the results in favour of ruxolitinib.

- The committee agreed with the EAG's correction to the estimation of utility for the non-response state in the company's model

- The committee considered that the company should incorporate utility and cost implications for adverse events present in 1% or more of people in any treatment group in the model, including those related to NB-UVB.

Specifically with regards to the economic analysis, the committee concluded that the company should amend its assumptions to include the following:

- removing vehicle cream and NB-UVB costs and assuming no dermatology visits in the non-response health state

- assuming 15% of people would have psychological support in each health state

- capping the utility values at general population values, and using a weighted average in the non-response health state of the values presented by the company for no response and having F-VASI 50 to 74

- applying costs in the non-response health state for a person's lifetime

- assuming missing data from the trials implied non-response when estimating the transition probability for people who have retreatment after relapse and do not regain response

- assuming either the dose of ruxolitinib was the mean value from the trials or people used the

- accepting the EAG's preferred assumptions on

    - removing vehicle cream costs

- the proportion of people having psychological support
- utility values in the non-response state
- using the mean dose of ruxolitinib in the model
- duration of costs in the non-response state
- accounting for missing data in calculating response rates on retreatment with ruxolitinib.

This document provides the EAG's critique of the company's response to the draft guidance produced by NICE for the appraisal of ruxolitinib for treating non-segmental vitiligo in people 12 years and older (ID3998).

In its response, the company presented additional data, including population characteristics and clinical effectiveness outcomes for those participants in the original trials who had received prior therapy and, specifically, prior TSC/TCIs. The company also provided changes to its economic model and a revised PAS discount for ruxolitinib. The EAG critique of the company's response is presented in Section 2. The EAG's preferred economic analyses are presented in Section 3.

2. EAG APPRAISAL OF THE REVISED COMPANY SUBMISSION

2.1. Critique of the company's definition of the decision problem

An overview of the EAG's critique of the company's definition of the decision problem in its re-submission is presented in Table 1, below.

As stated in the previous section, the NICE committee received advice from clinical experts that ruxolitinib would preferably be prescribed in primary care after a specialist diagnosis. However, in its resubmission, the company maintained that it wished to position ruxolitinib cream as a treatment option in secondary care. This had two important implications for the appraisal:

1. The Patient Access Scheme (PAS) discount for ruxolitinib cream would only apply if the appraisal committee chose to recommend ruxolitinib cream as a treatment option in secondary care.
2. The decision as to whether ruxolitinib cream would be prescribed in primary or secondary care would affect the relevant comparators to ruxolitinib cream.

With regard to the first of these, the company's economic analyses all included a PAS discount for ruxolitinib cream and the EAG analyses retained this. If the appraisal committee wished to consider a recommendation for ruxolitinib cream as prescribed from primary care, then the price of ruxolitinib cream would increase and the cost effectiveness analyses would require updating.

Secondly, and as described in the original EAG report, if ruxolitinib cream were to be prescribed in secondary care, then the appropriate comparator for ruxolitinib cream would be other second-line treatment options. For most people progressing to second line at the time, this would include NB-UVB therapy with or without TCS or TCIs. For those with rapidly progressing disease, the comparator would be betamethasone. As discussed in ACM1 for this appraisal, there was uncertainty surrounding how many people eligible for ruxolitinib cream would otherwise receive these other second-line treatment options, and therefore how to appropriately define the comparator arm for ruxolitinib cream. The appraisal committee requested that the company provide a comparison between ruxolitinib cream and NB-UVB, which the company provided within its resubmission.

Table 1: Summary of the decision problem

	Final scope issued by NICE	Decision problem addressed in the company's revised submission	EAG comment
Population	People aged 12 years and older with NSV with facial involvement	Adults and adolescents from 12 years of age with NSV with facial involvement for whom the disease has not responded to TCS or TCI, or for whom TCS or TCI are contraindicated, not tolerated or otherwise medically inadvisable.	The company submitted clinical effectiveness evidence for two subgroups of the trials: (a) participants who had previously received any treatment for vitiligo, and so were receiving ruxolitinib at 2nd + line; (b) participants who had previously received TCS or TCI. The company did not present evidence specifically for the target population, i.e. those who had not responded to TCS or TCI, or for whom TCS or TCI were contraindicated, not tolerated or otherwise medically inadvisable. The company did not state whether this was not possible for them to do based on the data collected in the trial. The EAG was uncertain whether a lack of response or a contraindication for TCS and TCI would affect response to ruxolitinib, although baseline disease characteristics of these subgroups presented in the re-submission suggested that, as a whole, those represented were experiencing disease severity comparable with the ITT population. In the company's revised analysis, the comparison with 'no active treatment', where the EAG placed most emphasis in its appraisal, used the term 'overall population', suggesting that the company used the ITT data in this analysis where outcomes could be expected to represent any treatment line.
Intervention	Ruxolitinib cream	Ruxolitinib cream	Aligned with the scope
Comparator(s)	Established clinical management without ruxolitinib cream	NB-UVB phototherapy	There was no evidence that provided a direct head-to-head comparison between ruxolitinib and NB-UVB phototherapy. In its original CS, the company stated that they had conducted a feasibility analysis and concluded that an indirect treatment comparison between ruxolitinib and NB-UVB phototherapy was not feasible. During its appraisal and as outlined in its report, the EAG reviewed the evidence base for NB-UVB and concluded that while an indirect treatment comparison and an unanchored MAIC could have been conducted to compare these treatments with the evidence available, the EAG agreed with the company that neither approach would present reliable estimates of the relative effectiveness of ruxolitinib as compared to NB-UVB.

	Final scope issued by NICE	Decision problem addressed in the company's revised submission	EAG comment
			In response to the NICE committee's preference to see a comparison between ruxolitinib and NB-UVB phototherapy, the company presented both an indirect treatment comparison (naïve comparison) and an unanchored MAIC. While the EAG acknowledged that the company had taken efforts to address the committee's wishes in providing these analyses, the EAG had little confidence in the results. Fundamentally, the EAG considered that the company's clinical trials of ruxolitinib were not relevant to the decision problem for the appraisal, and that statistical techniques could not address this or the lack of comparable studies for use in an indirect treatment comparison. Within the timeframe available to the company, it would evidently not have been possible for the company to identify new trial evidence that compared ruxolitinib and NB-UVB more robustly. However, this nevertheless resulted in a situation where there were no reliable estimates comparing ruxolitinib with NB-UVB.
Outcomes	The outcome measures to be considered include: • Re-pigmentation • Maintenance of response • Cessation of spread or stabilisation of vitiligo • Global assessment of vitiligo • Cosmetic acceptability • Adverse effects of treatment • Health related quality of life (HRQoL).	Incyte agrees that the suggested outcomes are appropriate, but notes that stabilisation of vitiligo was not captured in the TRuE-V[1] studies. However, Incyte deems that the endpoint of time to relapse (< F-VASI75) in the long-term treatment extension study (TRuE-V LTE[2]) adequately captures the maintenance of response to treatment.	Outcomes were reported for the two subgroups from the pooled TRuE-V1 and TRuE-V2 studies at 24 weeks only (excluding site 710). Outcome data were reported for the following outcomes: • Proportion of participants reaching F-VASI-50, F-VASI75, F-VASI90 • Proportion of participants reaching T-VASI-50 • Change in F-BSA • Proportion of participants reaching VNS 4/5 • Change from baseline in DLQI • Change from baseline in cDLQI These outcomes were consistent with most outcomes reported for the full trial populations in the CS, with the exclusion of the following: • Clinician- and patient-rated change in facial and total vitiligo

	Final scope issued by NICE	Decision problem addressed in the company's revised submission	EAG comment
			• VitiQoL • HADS • Treatment-emergent AEs Overall, the EAG considered that the outcomes reported were sufficient to reach a conclusion on the short-term effectiveness of ruxolitinib cream in comparison with vehicle cream, though noted the lack of safety data in the subgroups. The EAG also noted that clinical effectiveness data reported excluded any variance data, which limited some of the conclusions that could be drawn from the results.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. 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 Personal Social Services perspective.	As per the scope	Aligned with scope
Special considerations including issues related to equity or equality	Not included in the draft scope	No equality issues are foreseen in terms of providing ruxolitinib cream	The EAG did not identify any equality issues for this appraisal.

Abbreviations: BSA, body surface area; EAG, External Assessment Group; HRQoL, health-related quality of life; NB-UVB, narrowband ultraviolet B therapy; NICE, National Institute for Health and Care Excellence; NSV, non-segmental vitiligo; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids

2.2. EAG appraisal of the clinical effectiveness evidence submitted by the company

2.2.1. Design of the studies

The population subgroups presented in the updated company submission were defined and analysed post hoc from the TRuE-V1 and TRuE-V2 trials to align the evidence base with the company's selected target population. Data were presented for the double-blind phase of the trials only; i.e. data were available for up to 24-weeks of treatment in the two subgroups. Data were not presented for the open-label extension to the trials (continuation with or switch to ruxolitinib for a further 28 weeks) or for the long-term extension study.

2.2.2. Baseline characteristics

In its original report, the EAG stated that without baseline characteristics for the company's target population for ruxolitinib, the EAG was unable to rule out the possibility that population characteristics in the subgroup were influencing treatment outcomes. In its resubmission, the company presented key baseline characteristics for the two subgroups, with each treatment arm containing pooled data from the two trials, TRuE-V1 and TRuE-V2.

Baseline characteristics for the two subgroups appeared broadly comparable to those of the ITT population reported in the company's original submission and there were no evident differences between arms. While the EAG noted that the population subgroups were not wholly consistent with the company's target population for ruxolitinib (i.e. participants were not clearly stated to be unresponsive or intolerant to prior treatment), the EAG considered is plausible that the similarity of baseline disease outcomes could suggest that participants were not experiencing a satisfactory response to previous treatment, thus increasing the applicability of the data to the appraisal.

2.2.3. Intervention

The company provided new evidence for the dosage of ruxolitinib received by participants. These data are presented in further detail in Section 2.4.5. No details were provided about concomitant treatments received by participants in the subgroups.

2.2.4. Comparator

No further details were provided about the use of vehicle cream in the population subgroups, or any concomitant treatments received by participants in this arm.

2.2.5. Outcomes

The outcomes reported for the two population subgroups in the updated submission are shown in Table 2. All data were reported at 24 weeks. The outcomes reported for the ITT population in the original company submission but not reported for the population subgroups in the updated submission are crossed out. No explanation was provided by the company for the omission of these outcomes, the most significant of which were the absence of safety data. The EAG was uncertain whether those who had received previous treatment, and therefore may or may not have been unresponsive or intolerant to treatment, would have different safety risks compared to the ITT population.

Table 2: Clinical effectiveness outcomes reported for the two population subgroups in the updated submission

	Pooled TRuE-V1 and TRuE-V2 **Double-blind phase (24-weeks)**
Re-pigmentation	Facial and bodily vitiligo as assessed using F-VASI, F-BSA and T-VASI. ~~Clinician- and patient-rated change in facial and total vitiligo.~~
Maintenance of response	~~Change in F-VASI response~~
Cessation of spread or stabilisation of vitiligo	Facial and bodily vitiligo as assessed using F-VASI, F-BSA and T-VASI. ~~Clinician- and patient-rated change in facial and total vitiligo.~~
Global assessment of vitiligo	T-VASI ~~Clinician- and patient-rated change in total vitiligo~~
Cosmetic acceptability	VNS
Adverse effects of treatment	~~Treatment-emergent AEs~~
Health-related quality of life	~~VitiQoL (separate for each trial)~~ ~~HADS~~ DLQI and cDLQI

Abbreviations: AE, adverse events; cDLQI, children dermatology life quality index; DLQI, dermatology life quality index; F-BSA, facial body surface area; F-VASI Face Vitiligo Area Scoring Index score; HADS, hospital anxiety and depression scale; LSM, least squares mean; TCS, topical corticosteroids; TCI, topical calcineurin inhibitors; T-VASI, total body Vitiligo Area Scoring Index; VitiQoL, vitiligo-specific quality-of-life instrument; VNS, vitiligo noticeability score.

2.2.6. Critical appraisal

The company did not report an updated critical appraisal of the subgroup evidence in the updated submission or comment on any quality considerations specific to the subgroups. As noted above, the EAG did not find any indications that the break in randomisation for the subgroups had resulted in any meaningful differences in baseline characteristics between the subgroups and the ITT population or between arms. Without evidence to the contrary, the EAG chose to assume that the same quality issues that were relevant for the ITT population and discussed in the original EAG report applied to the subgroup evidence (i.e. that relative treatment effects may be more reliable than absolute effects, that there was a risk of a type 1 error due to multiplicity). However, the EAG acknowledged the company's explanation for anomalous dosing information in the original CS, which appeared to show that a minority of participants received a dose of ruxolitinib far in excess of the licensed dose (see Section 2.4.5), and no longer considered this as a risk of bias consideration.

2.2.7. Clinical effectiveness results

Clinical effectiveness results for the population subgroup are summarised in Table 3. The EAG noted that no variance data were presented to accompany the outcomes, including no confidence intervals to accompany the odds ratio (OR) data and no standard error or deviation to accompany the least squared mean (LSM) outcomes. The EAG considered this to be poor practice, as the variance data can provide an understanding of the certainty of an effect for decision-making. Moreover, no LSM was presented for cDLQI.

There was no difference between ruxolitinib and vehicle cream for quality of life as assessed using the DLQI: while there was a statistically significant difference between arms for those in the prior TCS/TCI group, the difference was below the threshold generally considered to be a minimally important difference on this measure.[3] However, all other outcomes showed large beneficial effects for ruxolitinib compared to vehicle cream. In general, larger effects were seen in the prior TCS/TCI group, though this was not universal across outcomes. Without confidence intervals, the EAG was unable to speculate on the extent to which the effects were comparable between subgroups and no statistical comparison was reported by the company. As in its original EAG report, the EAG was interested in the discrepancy between the large effects for the appearance of vitiligo and the lack of any difference in quality of life.

A comparison between the data presented for the subgroups and the ITT population suggested that the effects were slightly larger in the subgroups than in the ITT population, however no statistical comparison was reported.

Overall, after 24 weeks' of treatment and in the context of a double-blind trial in comparison with a placebo intervention (vehicle cream), the EAG concluded that ruxolitinib was highly effective in reducing facial, vitiligo, total vitiligo, and the cosmetic noticeability of vitiligo.

Table 3: Clinical effectiveness data reported for the two population subgroups

	Prior therapy (N=408)	**Prior TCS/TCI therapy (N=307)**
Proportion of participants achieving F-VASI75	OR = 4.60, p < 0.0001	OR = 5.62, p < 0.0001
Proportion of participants achieving F-VASI50	OR = 4.96, p < 0.0001	OR = 5.18, p < 0.0001
Proportion of participants achieving F-VASI90	OR = 11.38, p =0.0008	OR = 9.48, p = 0.0020
Proportion of participants achieving T-VASI50	OR = 4.40, p = 0.0003	OR = 4.67; p 0.0011
Percentage change from baseline in F-BSA	LSM -23.6, p < 0.0001	LSM -27.1, p < 0.0001
Proportion of participants achieving VNS 4/5	OR = 7.94, p < 0.0001	OR = 27.34, p = 0.0012
Change from baseline in DLQI	LSM -0.69, p=0.1272	LSM -1.66, p=0.0014
Change from baseline in cDLQI	Rux: 0.10 Vehicle: -1.17	Rux: 0.17 Vehicle: 1.00

Abbreviations: cDLQI, children dermatology life quality index; DLQI, dermatology life quality index; F-BSA, facial body surface area; F-VASI Face Vitiligo Area Scoring Index score; LSM, least squares mean; TCS, topical corticosteroids; TCI, topical calcineurin inhibitors; T-VASI, total body Vitiligo Area Scoring Index; VNS, vitiligo noticeability score.

2.3. Indirect treatment comparison

The company submitted methods information and results for an indirect treatment comparison (naïve) and a matching-adjusted indirect comparison (MAIC) that it conducted to compare

ruxolitinib with NB-UVB via the HI-LIGHT trial. As part of its original appraisal and as detailed in its report, the EAG considered whether either approach would be feasible to support the submission. This appraisal concluded that the HI-LIGHT trial was the best available evidence for NB-UVB that could be used in any indirect analysis, however that neither approach would result in reliable effect estimates of the comparison between ruxolitinib and NB-UVB. In sum, the EAG critique highlighted: variation in baseline characteristics between HI-LIGHT and the ruxolitinib trials; differences in baseline characteristics between arms of the small HI-LIGHT trial; discrepancies between the baseline characteristics reported for each trial that could be used in matching; and meaningful differences in the outcomes measured in each trial. The EAG therefore had no confidence in the results of the company's indirect treatment comparisons.

The EAG highlighted that the company had made significant effort to produce these analyses in the attempt to provide the committee with some evidence comparing the effectiveness of ruxolitinib cream with another treatment option available to people with vitiligo in the same positioning. The limitations in the comparability of the evidence for ruxolitinib and NB-UVB available for use in an indirect treatment comparison were beyond the control of the company at this stage of the appraisal. However, this did not change the reality that there were no reliable estimates for effectiveness of ruxolitinib cream in comparison with currently available alternatives. The EAG considered that a structured expert elicitation exercise to generate treatment effect estimates for NB-UVB (with and without corticosteroids) may have been a more reliable way of providing a comparison to ruxolitinib cream in the timeline available, despite the limitations of this approach. However, this approach may not have been feasible for the company, or it may not have considered that this approach would be acceptable to the committee. Overall, for the unknown number of people with vitiligo who would opt for NB-UVB therapy at second line, the EAG was unclear whether ruxolitinib would be more or less effective, and to what magnitude any difference in effect would be.

2.4. Summary and critique of the company's submitted economic evaluation

2.4.1. Population and comparators

In the original CS, ruxolitinib cream was compared only to vehicle cream, as a proxy for no active treatment. The company highlighted in its original submission that *"robust evidence synthesis for generation of treatment effect estimates for ruxolitinib cream relative to TCS, TCI or phototherapy was not feasible"* (CS, Section B.3.2.4, p.111). The appraisal committee highlighted in the DG that "*if ruxolitinib was to be prescribed in secondary care"* (confirmed to be

correct by the company in its response), then *"the relevant comparators would include phototherapy (with or without topical treatments) for people who are eligible for it and no active treatment for people who are not eligible for phototherapy"* (DG, Section 3.4, p.8).

In the company's response to DG, a total of four different comparisons were presented:

- 1: Ruxolitinib cream versus NB-UVB.
- 2: Ruxolitinib cream versus NB-UVB + TCS.
- 3: Ruxolitinib cream versus no active treatment followed by NB-UVB.
- 4: Ruxolitinib cream versus no active treatment.

The EAG acknowledged that these comparisons appeared to address the request made by the committee, but this did not necessarily mean that the comparisons made were sufficiently robust for decision making. As highlighted in Section 2.3, the EAG had no confidence in the results of the ITC comparing ruxolitinib cream to NB-UVB, with or without TCS. As such, while the EAG commended the company for attempting to make these comparisons, the EAG did not consider the results of comparisons 1 and 2 to be suitable for decision making.

For people who were not eligible for NB-UVB, the relevant comparator would be no active treatment (for which vehicle cream was assumed to serve as a proxy). The company highlighted in its response to DG that eligibility criteria for NB-UVB were not well-established, but that the key contributing factors to patients with NSV not undergoing NB-UVB may be (i) limited NHS resources, and (ii) patient choice, as opposed to a contraindication to phototherapy. The EAG agreed that it is difficult to qualify precisely which patients would be considered 'not eligible' for NB-UVB.

The company did not clearly state which of the four comparisons it provided it considered to best reflect the decision problem relevant to this appraisal, and the EAG noted that it would not be appropriate to consider comparisons within a fully incremental analysis (since the choice of comparator reflects different positionings of ruxolitinib cream). Taking a pragmatic viewpoint, the EAG expected that were ruxolitinib cream made available in NHS practice, many patients that would seek treatment were likely currently receiving no active treatment for NSV; however, some of these patients may in the future go on to receive NB-UVB. Therefore, for this reason, as well as the other issues affecting the ITC, the EAG focused its review on comparisons to no active treatment, which may or may not be followed by NB-UVB (i.e., comparisons 3 and 4).

2.4.2. Revised model

Following ACM1, the company made several changes to its original model, including model settings, assumptions, and input parameters. The EAG noted that the company elected to make all its edits in a version of the model where the EAG's previous edits had been removed, or in a version of the model which was either the same as, or similar to, the original model before the EAG's edits were made. This introduced two issues – first, that the EAG were unable to produce the company's original base-case, the company's revised base-case, and the EAG's previous base-case results all in one model file; and second, that without performing a cell-by-cell check (which was not feasible in the timeframe available to the EAG to provide its critique), the EAG were unable to verify that all changes made to the model had been made as described by the company.

The remainder of this sub-section describes the changes made by the company to its model.

2.4.3. Revised model structure

The company made some edits to the structure of its model following ACM1. Previously, initial response was assessed at 24 weeks, and people with at least a F-VASI 75 improvement would continue treatment. In the revised model, this threshold was changed to F-VASI 25 and was instead assumed to apply at 52 weeks. The EAG noted that the SmPC for ruxolitinib cream stated: *"Satisfactory repigmentation may require treatment beyond 24 weeks. If there is less than 25% repigmentation in treated areas at week 52, treatment discontinuation should be considered"* (SmPC, Section 4.2, p.2).[4] Depending on F-VASI response, patients would follow one of three 'routes' through the model:

- If an F-VASI 90 improvement occurred by week 52, patients transitioned directly to the 'stable' health state in which treatment was assumed to stop.
- If an F-VASI 25-89 improvement occurred by week 52, patients transitioned to the 'maintenance period' for an upper limit of a further 52 weeks of treatment. By the end of this second 52-week period of treatment, response was reassessed, and was now linked to the response achieved at week 52. If an F-VASI 90 improvement was observed, patients transitioned to the 'stable' health state where treatment was stopped. Else, if an F-VASI 90 improvement was not observed, then treatment was also stopped and patients transitioned to the 'non-response' state.

- If an F-VASI 25 improvement did not occur by week 52, then treatment was stopped and patients transitioned to the 'non-response' state.

From a face validity standpoint, the company's revised model served as an improvement on the previous model and addressed a number of concerns previously highlighted by the EAG and/or the committee. In particular, the EAG welcomed the structural edit made to the company's model wherein response was reassessed at week 104 and was tied to the initial response now measured at week 52 (instead of week 24). This meant that it was now structurally possible for patients to have a recorded F-VASI 90 response at week 104 when they did not originally have a recorded F-VASI 90 response at week 52. However, the revised model was not without limitations.

It was not immediately clear to the EAG how well the model represented what would happen in practice for people that have a minimal response to treatment by week 24. The EAG's clinical expert explained that in their practice, they would assess response every 3 to 4 months and look for around 20% improvement in re-pigmentation to justify continuing treatment. However, this was not how the company's model considered treatment continuation. It was not possible for the EAG to edit the transitions to explore alternative stopping criteria, as the latter aspects of the model relied on the link between response assessment at specific time intervals (i.e., week 52 and week 104).

The criteria used to justify retreatment, and subsequently continuation of treatment for those that are re-treated, differed markedly from the initial treatment period. Consistent with the company's original model, people in the 'stable' health state could experience depigmentation such that they are defined as having an F-VASI 75 or lower response, and this would trigger retreatment. The model then assumed that retreatment would stop for one of two reasons (excluding death): either (i) the patient was recorded as having an F-VASI 90 response again, and so would move to the 'stable retreated' health state, or (ii) the patient was recorded as not having an F-VASI 90 response again, and so would move to the 'non-response' health state.

As per the previous model, since patients were either F-VASI 90 or not F-VASI 90, in theory these criteria would mean patients instantly leave the 'retreated' health state. In reality, what was perhaps more likely to happen was that people would be treated for a given time period (such as 24 or 52 weeks), and then an assessment of response would take place to justify either continued treatment or discontinuation. However, likely due to difficulties in tracking patients over time in a Markov model, there was no explicit timing for the retreatment period.

The EAG therefore noted, as per the previous model, that this aspect of the model meant that the occupancy of the 'retreated' health state at any point in time reflected a people with divergent histories with respect to their response to treatment, and so a simplifying assumption to use static transition probabilities was likely flawed (though it was not possible for the EAG to determine in which direction results may be affected).

In addition, also in keeping with the EAG's critique of the previous model structure, patients were only permitted to undergo one course of retreatment with ruxolitinib cream, and the model mandated that patients receiving vehicle cream underwent retreatment in the same manner as per the ruxolitinib cream arm. The EAG did not consider retreatment to be a viable option for the comparator arm, and it expected that in clinical practice people with NSV may theoretically undergo many rounds of treatment with ruxolitinib cream over the course of their lives, yet the model did not account for this.

When considering the results of the company's revised model, it can be seen that the average additional time spent with F-VASI 90 was approximately doubled, which can also be observed based on a comparison of Markov traces for the ruxolitinib cream arm across the previous and latest model analyses from the company, as shown in Figure 1. Previously, at 1 year, approximately [redacted]% of people treated with ruxolitinib cream were assumed to be in non-response (i.e., off treatment), whereas in the company's revised model, approximately [redacted]% of people treated with ruxolitinib cream were assumed to be in non-response at 1 year.

Figure 1: Markov traces for company's original and revised models – ruxolitinib arm

Original

Revised

Note: Please interpret x-axis with caution – there may be some small misalignments owing to how stacked area charts are generated in Excel.

The EAG attempted to validate the proportion of patients with F-VASI 90 at key time points of Week 52 and Week 104 by comparing the estimated proportion of patients in the 'Stable' health state at these intervals with the estimated proportions from the TRuE-V1, -V2, and LTE trials. For the estimated proportions from the TRuE-V trials, the EAG used the following methodology:

- Week 52: As reported in CS Figure 11: n=106 of N=350 patients treated with ruxolitinib cream had achieved F-VASI 90 at week 52 (approximately 30.3%).
- Week 104: As reported in CS Section B.2.6.2.1: *"The majority of patients who achieved complete or near-complete repigmentation of the face (Cohort A, patients who had achieved F-VASI90 at Week 52) in the parent studies maintained this level of repigmentation with continued ruxolitinib cream application beyond Week 52; 61.8% of patients who applied ruxolitinib cream during the double-blind period and then continued treatment with ruxolitinib cream maintained at least 90% of facial repigmentation through Week 104."* Therefore, to crudely estimate the proportion of people with F-VASI 90 at Week 104, the EAG calculated 30.3% x 61.8% = 18.7%.

The EAG highlighted that this approach to estimating F-VASI 90 at Week 104, yielding a value of 18.7%, may be an overestimate since the model assumed that people that achieve F-VASI 90 at week 52 would discontinue treatment with ruxolitinib cream. Similarly, the TRuE-V trials did not include a stopping rule at Week 24 based on F-VASI 25, which would also remove a number of people from being able to obtain an F-VASI 90 response at either Week 52 or Week 104. In addition, not all patients were followed up to Week 104 for various reasons. Therefore, the value of 18.7% should be interpreted with these caveats in mind.

The resultant comparison is provided in Table 4.

Table 4: F-VASI 90 across both models and estimate from TRuE-V trials

Time	Original model	Revised model	TRuE-V
Week 52	[redacted]	[redacted]	30.3%
Week 104	[redacted]	[redacted]	18.7%

Abbreviations: F-VASI, facial vitiligo area scoring index; F-VASI90, 90% or greater improvement from baseline in F-VASI.

At Week 52, the company's revised model estimates a proportion of F-VASI 90 which is much closer to the TRuE-V trial estimate of 30.3%, compared to the company's original model. However, as noted previously, the EAG would expect the model to estimate a smaller proportion than the TRuE-V study owing to the specification of a stopping rule at Week 24 for those people that did not have at least an F-VASI 25 response.

Acknowledging that there were differences between model structures and how ruxolitinib cream was used in the TRuE-V trials versus expected NHS practice, the estimated proportions of people with F-VASI 90 at Week 104 are notably dissimilar. The company's revised model projected an additional 10% of people would achieve F-VASI 90 compared with the TRuE-V estimate of 18.7%. The EAG considered this result of the company's revised model to be unrealistic, since the proportion of people that would have F-VASI 90 at Week 104 in NHS practice was most likely lower than the TRuE-V estimate given that people would stop treatment at Week 52 if they had already achieved F-VASI 90.

Moreover, the EAG questioned the face validity of F-VASI 90 *increasing* from [redacted]% at Week 52 to [redacted]% at Week 104. This implies that a substantial number of people that previously did not have an F-VASI 90 response obtained an F-VASI 90 response through an additional 52 weeks of treatment with ruxolitinib cream, which more than offsets any people that no longer have an F-VASI 90 response at Week 104 despite having this at Week 52.

Overall, the EAG maintained that despite the company's revised model addressing some of the concerns previously raised by the EAG and/or the committee, it still had a number of important limitations. These related mostly to the face validity of the proportions of people in each response state over time and how retreatment was handled. Considered together, the EAG was concerned that the company's model under-estimated the costs of treatment with ruxolitinib cream over a lifetime horizon, and may have over-estimated the proportion of patients that obtained an F-VASI 90 response (at least over the course of the first two years of the model).

2.4.4. Utility values

Given the structural edits made to the company's model (see Section 2.4.3), the company also updated its utility analysis to ensure values could be estimated for all necessary F-VASI thresholds used to determine health state occupancy. In short, the company's revised utility analysis included an additional category for F-VASI25-49, which also impacted the 'No response' health state which previously included this group. The utility values used in the company's original model versus the company's revised model are presented in Table 5.

Table 5: Utility values used in company's original and revised model

Description	Original model	Revised model
No response	[redacted]	[redacted]
Baseline	[redacted]	[redacted]
F-VASI25-49	-	[redacted]
F-VASI50-74	[redacted]	[redacted]
F-VASI75-89	[redacted]	[redacted]
F-VASI90	[redacted]	[redacted]
Stable	[redacted]	[redacted]

Abbreviations: F-VASI, facial vitiligo area scoring index; F-VASI25-49 25% to 49% improvement from baseline in F-VASI; F-VASI50-74, 50% to 74% improvement from baseline in F-VASI; F-VASI75-89, 75% to 89% improvement from baseline in F-VASI; F-VASI90, 90% or greater improvement from baseline in F-VASI.

In its response, the company noted that the higher value for F-VASI25-49 versus F-VASI50-74 (as seen in Table 5) *"may be attributed to the inability to discriminate the difference in quality of life between the F-VASI25-49 and F-VASI50-74 response categories"* (Company's response, Section 2.9.1, p.52). The EAG noted that despite this observation, the values were applied without adjustment to inform the company's revised base-case analysis.

The EAG also noted the following features of the company's revised utility values:

- The original range of utility values (i.e., the difference between the smallest and largest value) was shorter ([redacted]), compared with the updated analysis ([redacted]). This meant that the company's revised model applied a relatively greater disutility for people that did not respond to treatment, as compared with the company's original model.
    - This was somewhat expected, since the 'No response' health state no longer included people with an F-VASI 25-49 improvement. However, the utility value estimated for F-VASI 25-49 did not exhibit face validity when considered alongside the other values, and so this called into question the face validity of the full set of utility values.
- The average utility for the age- and sex-adjusted general population aligned with the TRuE-V1 and TRuE-V2 trials was previously estimated by the EAG as approximately 0.908 (EAG report Appendix B). In the company's original model, the utility values for F-VASI75+

exceeded this value, whereas in the company's revised model, the utility values for F-VASI 25-49 and F-VASI75+ exceeded this value.

To address these issues with the company's revised base-case analysis, the EAG's revised base-case analysis included edits to ensure that (i) the utility value for F-VASI 25-49 was no greater than the utility value for F-VASI 50-74, and (ii) that no utility value could exceed the expected utility value for the age- and sex-adjusted general population. The EAG's preferred utility values are presented in Table 6, alongside the company's revised base-case analysis.

Table 6: Utility values used in company's and EAG's revised model

Description	Revised model (company)	Revised model (EAG)
No response	[redacted]	Per company value
Baseline	[redacted]	Per company value
*F-VASI25-49**	[redacted]	[redacted]
F-VASI50-74	[redacted]	Per company value
F-VASI75-89†	[redacted]	[redacted]
F-VASI90†	[redacted]	[redacted]
Stable†	[redacted]	[redacted]

Abbreviations: EAG, external assessment group; F-VASI, facial vitiligo area scoring index; F-VASI25-49 25% to 49% improvement from baseline in F-VASI; F-VASI50-74, 50% to 74% improvement from baseline in F-VASI; F-VASI75-89, 75% to 89% improvement from baseline in F-VASI; F-VASI90, 90% or greater improvement from baseline in F-VASI.

Notes: *Assumed to be same as F-VASI 50-74; †Assumed to be same as age- and sex-adjusted general population at baseline.

2.4.5. Ruxolitinib cream dosing

In the CS, ruxolitinib cream dosing was based on the observed median weight of the ruxolitinib cream and vehicle cream (combined) from the TRuE-V studies, at [redacted]g/day. The company caveated the justification for this initial dose by declaring it to be conservative, since "*clinicians described that compliance in clinical practice is expected to be lower than that of the trials*" (CS, Section B.3.5.1). Due to uncertainty around the dose which may be used in practice, alongside the large observed difference between the minimum and maximum dose in the TRuE-V studies, the EAG preferred to instead reflect the mean daily dose should the stated limit of two x 100 g tubes of ruxolitinib cream per month be adhered to in practice. As a consequence, the EAG's previous base-case analysis used either [redacted]g/day (one month defined to be 30.44 [2 d.p.] days)

or [redacted]g/day (one month defined to be 28.00 days). Each of these doses informed the two plausible, tentative EAG base case analyses.

Following ACM1, the appraisal committee's preference with respect to dosing was presented: *"The committee concluded that mean dose of ruxolitinib alone from the pooled TRuE-V trials should be used in the model, using appropriate methods to account for any missing data"* (DG, Section 3.9, p.14).

In response to DG, the company updated its dosing assumption to use the mean daily dose of ruxolitinib cream from the pooled TRuE-V studies rather than the median. In addition, the company explained that there were nine patients for whom missing data led to a likely over-estimate of the daily dose of ruxolitinib cream:

"The data from the pooled TRuE-V studies on ruxolitinib usage were limited by missing data for nine randomised patients (six patients treated with ruxolitinib 1.5% cream and three patients with vehicle cream) who discontinued study treatment and whose treatment duration was not recorded. For these nine patients, their duration of treatment was imputed as 1 day, with the total weight of drug applied assumed to be the same as their mean daily dose (which ranged between 117 g and 237 g)." (Company's response to DG, comment #6).

The revised mean dose which informed the company's base case was [redacted]g/day, where a lognormal distribution is explained to have been fitted to the TRuE-V trial dosing data in its entirety to avoid loss of information, while also accounting for the nine outliers from the study.

The EAG accepted that outliers may influence the estimation of the mean, however this information was not previously provided by the company (per appraisal timelines). In addition, although the company explained that a lognormal distribution was fitted to the data, the company's response to DG lacked numerical or graphical validation for this, as well as any assessment of statistical goodness-of-fit, therefore a clear rationale or sufficient justification as to why this transformation was applied was not apparent to the EAG.

The company also provided a new scenario in which the nine outlier patients were excluded from a simple re-calculation of the mean dose, leading to a value of [redacted]g/day. This remained a higher dose than in the original CS ([redacted]g/day), however without a revised median dose as a comparison, it was difficult to determine the relative impact of these outliers being excluded from the analysis.

Given a lack of validation for the choice of a lognormal distribution, in addition to a lack of data to suitably critique this, the EAG could only justify use of the revised non-parametric estimate of the mean within its preferred analysis, taking a value of [redacted]g/day.

The EAG highlighted that determining the true cost of ruxolitinib cream to the NHS was difficult to determine, since there were several factors that influenced the cost included in the model, which included (but are perhaps not limited to) the following:

- The overall intended use of ruxolitinib cream (e.g., facial only versus use over any affected areas of the body). Related to this point, the EAG noted that only facial benefits of re-pigmentation were directly captured by the company's model, though these are expected to represent the main benefits of treatment.
- How ruxolitinib cream would be dispensed (e.g., a monthly supply only, or potentially several months' supply at a time in keeping with assessment milestones).
- How retreatment would be considered in NHS practice, including the potential for people to seek treatment over a lifetime versus the two-course limit currently imposed by the company's model.

2.4.6. Medical resource use costs and assumptions

The original CS included a proposed list price for one tube of ruxolitinib cream of £[redacted] (100g), with an estimated daily dose of [redacted]g. This equated to a cost per day of £[redacted], shown in Table 29 of the CS. A revised list price and PAS discounted were later proposed by the company, and included in its revised model. The revised list price for one tube of ruxolitinib cream was £[redacted], and a [redacted]% simple PAS discount was now applied, making the effective ruxolitinib cream price per tube £[redacted]. The EAG agreed with the appraisal committee that a cost of £0 should be applied for no active treatment (previously referred to as 'vehicle cream') in the model, rather than costing this as sunscreen per the original CS.

The company's revised model made changes to the costing of NB-UVB in line with the presentation of four comparisons (see Section 2.4.1). However, the EAG had concerns with respect to producing direct comparisons to NB-UVB (see Section 2.3), and so preferred to consider NB-UVB as a downstream cost. Per the DG, the company's revised model assumed that 25% of people would ultimately receive NB-UVB treatment, which the EAG considered a reasonable assumption to reflect current NHS practice. Nevertheless, the EAG maintained that

NB-UVB would ideally be considered a comparator, though the EAG accepted that current evidence did not allow for such a comparison to be robustly established.

The company's updated disease management assumptions have been provided in Table 9 to align with the appraisal committee's preferences in ACM1. In brief, these changes meant that:

- Dermatologist nurse visits and telephone consultations were set to 0% for people that did not respond to treatment.
- Monitoring in secondary care by a dermatologist for people that did not respond to treatment was reduced to 15%.
- All health states included 15% of people accessing psychological support services.

Together, the EAG believed that these assumptions were more plausible versus the original CS.

2.4.7. Company's revised cost-effectiveness results

A revised base-case analysis was presented by the company in its response to DG. As noted previously, the EAG opted to focus its critique on the comparison against no active treatment. However, for completeness, the company's revised base-case analysis comparing ruxolitinib cream to NB-UVB, with or without TCS, suggested that ruxolitinib cream would be cost saving and provide more QALYs (i.e., that ruxolitinib cream dominates NB-UVB). The EAG had no robust evidence base from which to assess the face validity of this result, though as described previously, the EAG considered that the clinical evidence used to inform this analysis was potentially flawed.

The EAG highlighted that the projected QALY gains across each of the four comparisons made by the company were notably similar (range: [redacted] to [redacted]), which the EAG did not consider realistic. Instead, the EAG would expect that the modelled QALY gain for ruxolitinib cream versus NB-UVB, assuming that ruxolitinib cream afforded a QALY advantage, would be smaller than the QALY gain versus no active treatment (since the British Association of Dermatologists [BAD] guidelines included a strong recommendation for the use of NB-UVB).[5] From a cost perspective, the EAG was concerned that the model likely reflected an under-estimation of the expected use of ruxolitinib cream over a lifetime.

Reverting to the comparisons against no active treatment, the company's base-case results are provided in Table 7, for comparisons against no active treatment followed by NB-UVB and no

active treatment not followed by NB-UVB. For ease of comparison, the company's corrected base-case results from its previous model are provided in Table 8.

Table 7. Company's revised base-case results

Arm	Total discounted		Incremental discounted		Cost per QALY gained
	Costs	QALYs	Costs	QALYs	
No active treatment followed by NB-UVB					
No active treatment	[redacted]	[redacted]	-	-	-
Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	£18,103
No active treatment alone					
No active treatment	[redacted]	[redacted]	-	-	-
Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	£20,018

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life year(s).

Table 8. Company's previous base-case results

Arm	Total discounted		Incremental discounted		Cost per QALY gained
	Costs	QALYs	Costs	QALYs	
No active treatment	[redacted]	[redacted]	-	-	-
Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	£13,481

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life year(s).

The company's revised base-case analysis projected a QALY gain which was close to three-times that of the company's previous base-case analysis ([redacted] versus [redacted]) and assumed that patients spend approximately twice the amount of the time in F-VASI90 (0.920 versus 0.461 years). The company did not present any validation exercises to support these substantial changes to the results of its modelling, nor did it provide any clear justification in its response. In addition, the company's revised model continued to assume that subsequent use of NB-UVB had no impact on utility.

3. EAG PREFERRED BASE CASE AND EXPLORATORY ANALYSES

3.1. EAG's tentative preferred base-case analysis

As noted in Section 2.4.2, the company's revised analysis was produced in a version of the model where the EAG's previous analyses had been removed. For this reason, and the other limitations of the company's revised model highlighted throughout Section 2.4, the EAG could only provide a tentative preferred base-case analysis, starting from the company's revised base-case analysis.

The company's response to DG included four different comparisons, as discussed in Section 2.4.1. The EAG focused its tentative preferred base-case on comparison 3 (versus no active treatment followed by NB-UVB) for the following reasons:

- Comparisons 1 and 2 (versus NB-UVB, with or without TCS) rely on an ITC which the EAG does not consider suitable for decision-making (see Section 2.3).
- Comparison 4 (versus NB-UVB followed by no NB-UVB) did not represent current NHS practice where NB-UVB was available (though was not utilised by all people with NSV), and the ICER for comparison 3 was slightly lower than comparison 4. The EAG expected that any ICER generated for comparison 3 could be assumed to represent a lower bound for a corresponding ICER for comparison 4.

The EAG's tentative preferred base-case analysis, using comparison 3, included the following changes made to the company's revised base-case analysis:

- F-VASI 25-49 utility value assumed to be the same as F-VASI 50-74.
- All utility values capped by general population estimates.
- Dose of ruxolitinib cream changed to non-parametric mean estimate, excluding nine outlier patients identified by the company.

The individual and combined effects of these changes on the company's revised base-case analysis is provided in Table 9.

Table 9. EAG's tentative preferred base-case results

Arm	Total discounted		Incremental discounted		Cost per QALY gained
	Costs	QALYs	Costs	QALYs	
Company's revised base-case analysis (Comparison 3)					
No active treatment	[redacted]	[redacted]	-	-	-
Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	£18,103
1: Comparison 3 + F-VASI 25-49 utility value set equal to that of F-VASI 50-74					
No active treatment	[redacted]	[redacted]	-	-	-
Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	£18,154
2: Comparison 3 + all utility values capped by general population utility estimates					
No active treatment	[redacted]	[redacted]	-	-	-
Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	£21,798
3: Comparison 3 + set ruxolitinib cream dose to the revised mean, [redacted]g					
No active treatment	[redacted]	[redacted]	-	-	-
Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	£21,400
1 + 2 + 3 (As above): EAG's tentative preferred base-case analysis					
No active treatment	[redacted]	[redacted]	-	-	-
Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	£25,856

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life year(s).

The EAG's tentative preferred base-case only includes the changes provided in Table 9. The updated model still captured multiple rounds of retreatment in addition to assuming a lower utility value for people in the non-response health state compared to baseline, both of which are further discussed and explored throughout Section 3.2. Although separately adjusting these settings impacted the cost-effectiveness of ruxolitinib cream, the EAG believed that these scenarios should remain as exploratory as a means of highlighting the sensitivity of the ICER.

3.2. EAG's exploratory analyses

To add further context to the EAG's tentative preferred base-case analysis, the EAG sought to further understand the costs related to retreatment, and utility for the non-response state.

3.2.1. Retreatment for the no active treatment arm

In the company's revised base-case analysis, retreatment was applied for 100% of patients in both treatment arms. Disabling retreatment for both arms caused the ICER to increase from

£18,303 to £21,919. However, retreatment was applied for both treatment arms, despite 'no active treatment' being the comparator of interest. As an exploratory analysis, the EAG compared the ruxolitinib cream arm with retreatment enabled to the no active treatment arm with retreatment disabled, with results presented in Table 10.

Table 10. Exploratory analysis: retreatment disabled for no active treatment arm only

Arm	Total discounted		Incremental discounted		Cost per QALY gained
	Costs	QALYs	Costs	QALYs	
Company's revised base-case analysis					
No active treatment	[redacted]	[redacted]	-	-	-
Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	£18,103
Exploratory analysis: Retreatment disabled for both arms					
No active treatment	[redacted]	[redacted]	-	-	-
Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	£21,919
Exploratory analysis: Retreatment disabled for no active treatment*					
No active treatment	[redacted]	[redacted]	-	-	-
Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	£17,726

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life year(s).

Note: *This result cannot be directly obtained in the company's revised model, but can be inferred by combining results with and without retreatment enabled.

The results presented in Table 10 showed that when disabling retreatment for the no active treatment arm, total costs and total QALYs reduced slightly, meaning that the ICER improved. The EAG considered this scenario to be more reflective of retreatment in practice, but the functionality of the model did not easily allow for this to be programmed in separately for each treatment arm, hence its consideration here as an exploratory analysis only.

3.2.2. Isolating the costs and benefits of retreatment with ruxolitinib cream

As shown in Table 10, disabling retreatment for both treatment arms caused the ICER to increase, but disabling retreatment only for the no active treatment arm caused the ICER to decrease. The EAG considered it potentially useful to understand the differences in costs and outcomes between analyses that include or exclude retreatment.

When setting discount rates for costs and outcomes to 0%, setting all non-ruxolitinib cream costs to zero, and comparing models with retreatment enabled and disabled, retreatment was

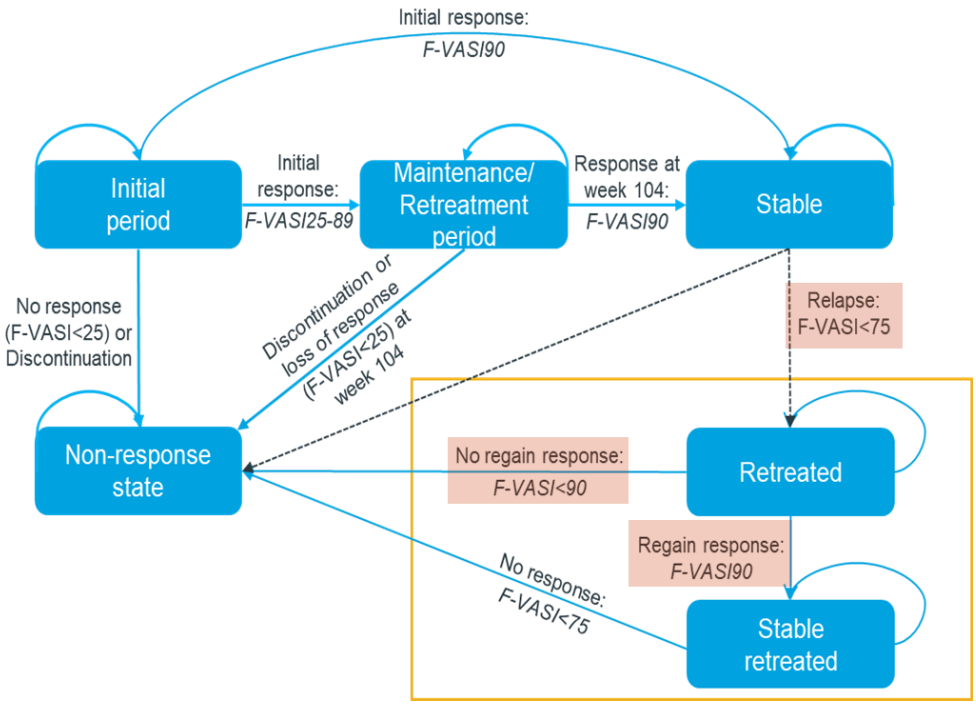
associated with an additional cost of £[redacted] and an additional QALY gain of [redacted] applied to the ruxolitinib cream arm. This can then be compared to the total costs and QALYs gained for the first course of treatment, which are £[redacted] and [redacted], respectively. When comparing these values to the incremental costs and QALYs versus no active treatment, it was seen that retreatment was suggested to provide about one-third of the QALYs gained for the first course of treatment, at a cost of around 8% of the first course of treatment.

The EAG questioned the face validity of this estimate, since it implied that relatively few patients are re-treated (where costs can be used as a proxy for the relative uptake of retreatment), but retreatment was associated with a (relatively) large QALY gain. Based on the EAG's inspection of the company's revised model, it appeared that over the lifetime horizon of the company's model, approximately [redacted]%* of patients would initiate retreatment at some stage, which is similar to the ratio of QALYs. The benefit of retreatment was therefore assumed to be essentially on par with the benefit of the first course of treatment, but at about [redacted] of the cost.

To understand this further, the EAG directed attention to the company's revised model schematic, of which an annotated copy is provided in Figure 2. The red shaded boxes were added by the EAG, denoting the criteria used to determine which patients can be retreated, and how they are later determined to exit the retreatment health state.

* This value was estimated by calculating the product of occupancy of the 'Stable' health state across all model cycles and the transition probability 'relap_r_Inter'.

Figure 2: Company's revised model schematic



Abbreviations: F-VASI, facial vitiligo area scoring index.

Note: Dead, not presented in the figure for simplicity, is an absorbing state and can be reached from any of the other health states. In the maintenance/retreatment period, patients initiated on ruxolitinib 1.5% cream or no active treatment continue those treatments, while those initiated on NB-UVB receive an additional course of NB-UVB.

Source: Adapted from Company's response to Draft Guidance, Figure 5 of Appendix A.

Related to the company's model schematic, the EAG noted the following:

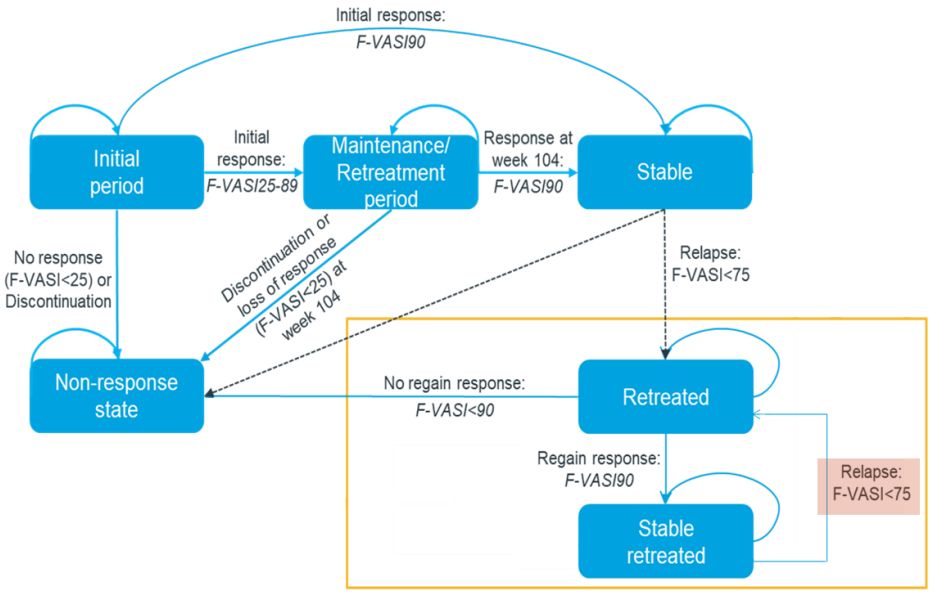
- All people that previously obtained an F-VASI 90 response were assumed to be retreated, and that this was triggered immediately once response dropped to F-VASI 75.
- Retreatment was stopped for one of three reasons:
  - An F-VASI 90 response was not obtained, and so patients moved to 'No response'.
  - An F-VASI 90 response was obtained, and so patients moved to 'Stable retreated' (and discontinued treatment).
  - Death.

These features of the company's model illustrated why there was a notable difference in costs and benefits between the initial treatment and retreatment periods. Patients that were re-treated in the model represented a selected sample of people for whom previous treatment led to an F-VASI 90 response up to *at least* 52 weeks (for those with an initial F-VASI 90 response) or 104 weeks (for those that initially obtained an F-VASI 25-89 response, which later improved to F-VASI 90). For those people that did not achieve an F-VASI 90 following initiation of retreatment, treatment was assumed to stop. It was not clear to the EAG how reasonable this probability of not responding to retreatment was to apply in the model given the updated treatment stopping rules. For example, it was the EAG's understanding that a person could be re-treated for a period of 104 weeks provided that they maintain a minimum response of F-VASI 25, but this concept was not captured in the retreatment period.

3.2.3. Allowing for infinite courses of retreatment

It was theoretically possible to re-wire the company's model to instead route patients back to retreatment instead of no response after relapse, and so the EAG explored the impact of doing this. A revised schematic of the company's model is provided in Figure 3, alongside results of the company's base-case analysis in Table 11. If patients were re-routed to retreatment indefinitely (subject to the re-obtaining F-VASI 90, the model time horizon, and mortality), then the QALY gain increased substantially, leading to an ICER of £3,037.

Figure 3: EAG's exploratory edit of the company's revised model



Abbreviations: F-VASI, facial vitiligo area scoring index.
Note: Dead, not presented in the figure for simplicity, is an absorbing state and can be reached from any of the other health states. In the maintenance/retreatment period, patients initiated on ruxolitinib 1.5% cream or no active treatment continue those treatments, while those initiated on NB-UVB receive an additional course of NB-UVB.
Source: Adapted from Company's response to Draft Guidance, Figure 5 of Appendix A.

Table 11. Exploratory analysis: infinite retreatment for ruxolitinib arm

Arm	Total discounted		Incremental discounted		Cost per QALY gained
	Costs	QALYs	Costs	QALYs	
Company's revised base-case analysis					
No active treatment	[redacted]	[redacted]	-	-	-
Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	£18,103
Exploratory analysis: Infinite retreatment enabled for ruxolitinib cream					
No active treatment	[redacted]	[redacted]	-	-	-
Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	£3,037

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life year(s).

For the avoidance of doubt, the EAG did not consider the exploratory analysis results presented in Table 11 to be a suitable basis to inform decision-making, as the results did not exhibit face validity. However, these findings may be helpful when considering the impact of retreatment on model results. For example, the results showed that including more retreatment in this version of the model would improve the ICER, but this did not mean that the current retreatment settings are reflective of the costs and outcomes associated with retreatment per expected use in NHS practice.

3.2.4. Utility for the non-response state

In the company's revised model, the baseline utility value for patients was estimated to be [redacted], whereas the utility for the 'no response' health state was estimated to be [redacted]. The EAG previously highlighted concerns with this apparent discrepancy in methodology and values for the baseline and no response utility values (see EAR Section 4.2.8). It was the EAG's view that the difference between the baseline and no response utility values may be greater than what would be expected, since some patients in the no response health state may technically have better utility versus baseline (if, for example, they have had a modest F-VASI improvement). To explore this further, the EAG considered the following additional exploratory analyses:

- Set no response utility value to be the same as the baseline utility value ([redacted]).
- Set no response utility value to be half-way between the current baseline and no response utility values ([redacted]).

The results of these exploratory analyses are presented in Table 12, alongside the company's revised base-case analysis.

Table 12. Exploratory analysis: utility value for no response

Arm	Total discounted		Incremental discounted		Cost per QALY gained
	Costs	QALYs	Costs	QALYs	
Company's revised base-case analysis					
No active treatment	[redacted]	[redacted]	-	-	-
Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	£18,103
Exploratory analysis: No response utility same as baseline ([redacted])					
No active treatment	[redacted]	[redacted]	-	-	-
Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	£60,336
Exploratory analysis: No response utility average of no response and baseline ([redacted])					
No active treatment	[redacted]	[redacted]	-	-	-
Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	£27,850

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life year(s).

While exploratory, the EAG highlighted that these analyses demonstrated the sensitivity of how much utility was expected to decline for people that did not respond to treatment with ruxolitinib cream. The group of people that did not respond was expected to comprise a mixture of those with a modest improvement, those with no improvement, and those with worsened de-pigmentation.

In addition, if the general population capping was also applied to the first exploratory analysis presented in Table 12, the resultant ICER would be £138,696.

4. CONCLUSIONS OF THE EAG APPRAISAL

The clinical effectiveness evidence presented by the company for the previously treated subgroups, while not without some limitations, demonstrated that ruxolitinib was highly effective at improving facial vitiligo, total vitiligo, and the cosmetic noticeability of vitiligo after 24-weeks' of treatment. The company did not present evidence for the safety or long-term effects of ruxolitinib in the previously treated population, though the EAG was not aware of any evidence to suggest that meaningfully different estimates would be expected than those reported in the original CS for the ITT population. There was no evident effect of treatment with ruxolitinib cream on participants' quality of life. While the EAG acknowledged the effort made by the company to provide estimates of the efficacy of ruxolitinib cream in comparison with NB-UVB, the EAG concluded that reliable treatment effect estimates for ruxolitinib were only available for patients in whom NB-UVB was not an option. This affects an unknown proportion of the target population, given uncertainties about the number of people who would be eligible for NB-UVB.

With respect to cost effectiveness, the EAG was concerned that the company's revised model over-estimated the benefits and under-estimated the costs of ruxolitinib cream through the following mechanisms:

- Time spent in F-VASI 90 may be unrealistic – see Section 2.4.3.
- Utility gains were likely inflated due to some utility values being greater than those for the age- and sex-adjusted general population, as well as the broader spread of utility values across the different response categories – see Section 2.4.4.
- Only one course of retreatment was permitted by the model, despite there being no apparent upper limit for treatment courses in expected NHS practice – see Section 2.4.5.

Taken together, alongside the EAG's tentative revised base-case analysis, the most likely ICER was expected to be greater than the range normally considered to represent a cost-effective use of NHS and PSS resources.

5. REFERENCES

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