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:

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

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

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Vitiligo Society
   b. Vitiligo Support UK
   c. British Association of Dermatology *endorsed by the Royal College of Physicians*

4. **Expert personal perspectives** from:
   a. Dr Jonathan Batchelor, Consultant Dermatologist; Clinical Lead for Dermatology (PRUH and South Sites) – clinical expert, nominated by Vitiligo Support UK
   b. Dr Viktoria Eleftheriadou, Consultant Dermatologist; Associate Professor – clinical expert, nominated by British Association of Dermatologists (BAD)
   c. Emma Rush, CEO of Vitiligo Support UK – patient expert, nominated by Vitiligo Support UK
   d. Pav Korpal – patient expert, nominated by Vitiligo Support UK

5. **External Assessment Report** prepared by Peninsula Technology Assessment Group (PenTAG)

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

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Document B

Company evidence submission

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ID3998_ruxolitinib cream_STA_Document B	**V1.0**	**Yes**	**10th August 2023**

Contents

Tables

Figures

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

B.1.1 Decision problem

The marketing authorisation for ruxolitinib 1.5% cream (Opzelura) is for the treatment of non-segmental vitiligo (NSV) with facial involvement in adults and adolescents from 12 years of age. [redacted](1).

This submission focuses on a sub-population of the health technology's licensed population, that is, adults and adolescents from 12 years of age with NSV with facial involvement for whom the disease has not responded to topical corticosteroids (TCS), topical calcineurin inhibitors (TCI), or for whom TCS or TCI are contraindicated, not tolerated or otherwise medically inadvisable. This is narrower than the marketing authorisation because:

- This position is more relevant to the National Health Service (NHS) clinical practice, as we anticipate ruxolitinib cream to be positioned as a step change option after considering treatment with TCS or TCI
- This reflects a position where ruxolitinib cream provides the most clinical benefit for patients with the highest unmet need in England and Wales

As the first licensed treatment for NSV, ruxolitinib cream addresses an unmet need by offering a tolerable and effective treatment for what has to date been a chronically neglected and underserved patient population.

The company submission is broadly consistent with the final National Institute for Health and Care Excellence (NICE) scope and is consistent with the NICE reference case (see **Table 1**).

The evidence for this appraisal is derived from the TRuE-V1 and TRuE-V2 randomised controlled trials (RCTs) that evaluated the efficacy and safety of ruxolitinib cream in adolescent and adult participants with NSV for whom total body involved vitiligo area (facial and non-facial) does not exceed 10% body surface area (BSA) (2, 3), in addition to the TRuE-V long-term extension (LTE) trial that assessed the long-term efficacy and safety of ruxolitinib cream in participants with vitiligo (4).

This submission addresses the cost-effectiveness, clinical efficacy, and safety of ruxolitinib cream for NSV in adults and adolescents from 12 years of age.

Having received its marketing authorisation from MHRA in July 2023, ruxolitinib cream is currently the only approved treatment for vitiligo (5, 6). To date, patients receiving therapy for treatment of vitiligo use off-label treatments, which consist of TCS, TCI, phototherapy, laser therapy, topical vitamin D analogues, and a combination of phototherapy with TCI/TCS (7-9). Off-label treatments used for vitiligo such as TCS, TCI and phototherapy have well-known risks and limitations for their use in vitiligo, including limited evidence for efficacy and long-term safety (10, 11), low compliance (12, 13), and limited tolerability (9, 14-17).

Ruxolitinib cream is anticipated to be positioned as a step change option between first and second line (7) for adults and adolescents from 12 years of age with NSV with facial involvement for whom the disease has not responded to TCS, TCI, or for whom TCS or TCI are contraindicated, not tolerated or otherwise medically inadvisable. Therefore, TCS, TCI and phototherapy are not relevant comparators. Notwithstanding this positioning in the treatment pathway, an assessment was conducted to also investigate the feasibility of deriving treatment effect estimates for ruxolitinib cream relative to TCS, TCI and phototherapy. The indirect treatment comparison (ITC) feasibility assessment (FA) found that there is an insufficient evidence base to robustly compare the efficacy of ruxolitinib cream to existing off-label therapies. The lack of comparable studies is partly due to an evolving set of tools that are used to evaluate vitiligo treatments. In addition, most of the clinical studies were of low methodological quality. Details of the ITC are presented in section B2.9 and in Appendix D.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
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.	Not applicable – as per the final scope
Intervention	Ruxolitinib cream	Ruxolitinib cream	Not applicable – as per the final scope
Comparator(s)	Established clinical management without ruxolitinib cream	Vehicle cream	To date, established clinical management involved the use of off-label treatments, which consist of TCS, TCI, phototherapy, laser therapy, topical vitamin D analogues, and a combination of phototherapy with TCI/TCS (7-9). Ruxolitinib cream is anticipated to be positioned as a step change option between first and second line (7) for adults and adolescents from 12 years of age with NSV with facial involvement for whom the disease has not responded to TCS, TCI, or for whom TCS or TCI are contraindicated, not tolerated or otherwise medically inadvisable. Therefore, TCS, TCI and phototherapy are not relevant comparators. Given the lack of treatment alternatives in the anticipated positioning, vehicle cream as investigated in the double-blind phase of the TRuE-V trials is an appropriate comparator for the appraisal of ruxolitinib cream.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			Notwithstanding this positioning in the treatment pathway, an ITC FA was conducted to also investigate the feasibility of deriving treatment effect estimates for ruxolitinib cream relative to TCS, TCI and phototherapy. The ITC FA found that there is an insufficient evidence base to robustly compare the efficacy of ruxolitinib cream to existing off-label therapies.
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 studies. However, Incyte deems that the endpoint of time to relapse (< F-VASI75) in the long-term treatment extension study (TRuE-V LTE) adequately captures the maintenance of response to treatment.	Not applicable
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.	As per the final scope	Not applicable

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	Costs will be considered from an NHS and Personal Social Services perspective.		
Subgroups to be considered	Not included in the draft scope	Due to the anticipated positioning of ruxolitinib cream, the subgroup "prior therapy" is used in the base case, and additional analyses are presented using the intention-to-treat (ITT) population and the subgroup "Fitzpatrick Skin Type IV-VI".	Vitiligo is more noticeable in people with darker skin tones and associated with higher disease burden (18), therefore differential cost-effectiveness is expected in this subgroup. A request was made during the decision problem meeting that Incyte presents this subgroup analysis.
Special considerations, including equity or equality issues	Not included in the draft scope	No equality issues are foreseen in terms of providing ruxolitinib cream	Although vitiligo is more noticeable in people with darker skin tones, as noted in the draft scope, and while we expect differential cost-effectiveness in this subgroup due to the different impact of repigmentation on HRQoL, Incyte aims to make ruxolitinib cream available for all patients. Therefore, no equality issues are foreseen in terms of providing ruxolitinib cream to eligible patients, including adults and adolescents from 12 years of age.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	Ruxolitinib cream is the first treatment to be licensed specifically for NSV with facial involvement. Incyte notes that the lack of specific standardised outcomes for vitiligo prior to the design of the TRuE-V clinical development programmes resulted in challenges in stratifying the severity of vitiligo.	Not applicable

Abbreviations: BSC, best supportive care; F-VASI75; NHS, national health service; NICE, National Institute for Health and Care Excellence; TCI, topical calcineurin inhibitors; TCS; topical corticosteroids; TRuE-V, topical ruxolitinib evaluation in vitiligo; LTE, long-term extension; UK, United Kingdom.

B.1.2 Description of the technology being evaluated

Ruxolitinib cream's mechanism of action, marketing authorisation, indication, mode of administration and list price are summarised in **Table 2**. Appendix C includes the summary of product characteristics (SmPC) for ruxolitinib cream.

Table 2. Technology being evaluated

UK approved name and brand name	Ruxolitinib 1.5% cream (Opzelura®)
Mechanism of action	Ruxolitinib is a Janus Kinase (JAK) inhibitor with selectivity for the JAK1 and JAK2 isoforms. Intracellular JAK signalling involves the recruitment of signal transducers and activators of transcription (STATs) to cytokine receptors, and subsequent modulation of gene expression. Autoimmune IFNγ-producing cytotoxic T lymphocytes are thought to be directly responsible for melanocyte destruction in human vitiligo. Recruitment of cytotoxic lymphocytes to lesional skin is mediated via IFNγ dependent chemokines, such as CXCL10. Downstream signalling of IFNγ is JAK1/2 dependent, and treatment with ruxolitinib reduces CXCL10 levels in vitiligo patients (19).
Marketing authorisation/CE mark status	Ruxolitinib cream received MHRA approval on 04th July 2023
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Ruxolitinib cream is indicated for the treatment of NSV with facial involvement in adults and adolescents from 12 years of age (19).
Method of administration and dosage	The recommended dose is a thin layer of cream applied twice daily to the depigmented skin areas up to a maximum of 10% of BSA, with a minimum of 8 hours between two applications ruxolitinib cream. 10% BSA represents an area as large as the back of two hands and the face. No more than two tubes of 100 grams a month should be used (19). Satisfactory repigmentation may require treatment beyond 24 weeks. If there is less than 25% repigmentation in treated areas at week 52, treatment discontinuation may be considered. There is no need to consider tapering therapy (19).
Additional tests or investigations	None.
List price and average cost of a course of treatment	[redacted] per 100g tube[redacted]. The average cost for a course of treatment (21.4 months of treatment) is [redacted]
Patient access scheme (if applicable)	Incyte has submitted a patient access scheme for consideration as part of this appraisal.

Abbreviations: BSA, body surface area; CE, conformité Européenne; CXCL10, chemokine interferon-γ inducible protein 10 kDa[redacted]; IFNγ, interferon-gamma; JAK, janus kinase; MHRA, Medicines and Healthcare products Regulatory Agency; NSV, non-segmental vitiligo; STATs, signal transducers and activators of transcription.

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

B.1.3.1 Disease overview

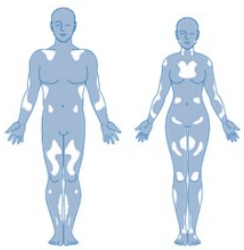
Vitiligo is a chronic autoimmune skin disease which results in patches of depigmentation (visible loss of skin colour) due to the progressive loss of melanocytes (skin cells) (5, 8, 20, 21). In patients with vitiligo, the disease appears as distinct white, non-scaly skin lesions (20).

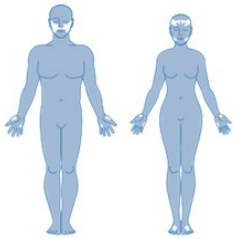
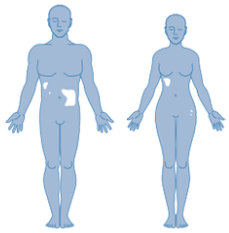
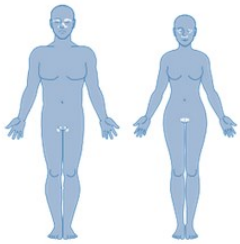
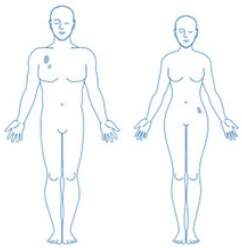
Non-segmental vitiligo

NSV is an umbrella term, which encompasses most forms of vitiligo experienced by patients, including generalised, acrofacial (affecting the extremities and the face), mucosal, and universal (20, 22) (**Table 3**). Generalised and acrofacial vitiligo are the most common forms of NSV (20). NSV generally progresses slowly and has an unpredictable course involving multiple flare-ups (20, 22, 23); it arises from an autoimmune attack on functional melanocytes (5, 8, 20, 22).

NSV is the most common form of vitiligo, which accounts for 80% of cases of vitiligo (24). NSV may have an early onset (<12 years of age), and onset peaks at around 30 years of age (20).

Table 3. Classification of NSV

Subtype	Description
Generalised or common[b] 	Macules/patches are often symmetrical; it can affect any part of the skin, mainly hands, fingers, face, and trauma-exposed areas (formerly known as vulgaris)
Acro-facial[a]	Affects the face, head, hands, and feet, and typically involves the perioral region and the extremities of digits

Subtype	Description
	
Focal[a] 	Small and isolated lesions with no obvious pattern which do not usually evolve for long periods (1–2 years)
Mucosal[a] 	Affects the genital and oral mucosae. Furthermore, areas of mucosa may also be affected in patients with acrofacial, common, or universal forms
Universal[a] 	Affects the largest extent of the skin (80–90% of the body surface) and usually occurs in adulthood. The generalised or common form usually precedes it

[a]Images created by Teitge Design (www.teitgedesign.com/); original available at https://www.umassmed.edu/vitiligo/blog/blog-posts1/2020/05/patterns-of-vitiligo/. Accessed August 2023.

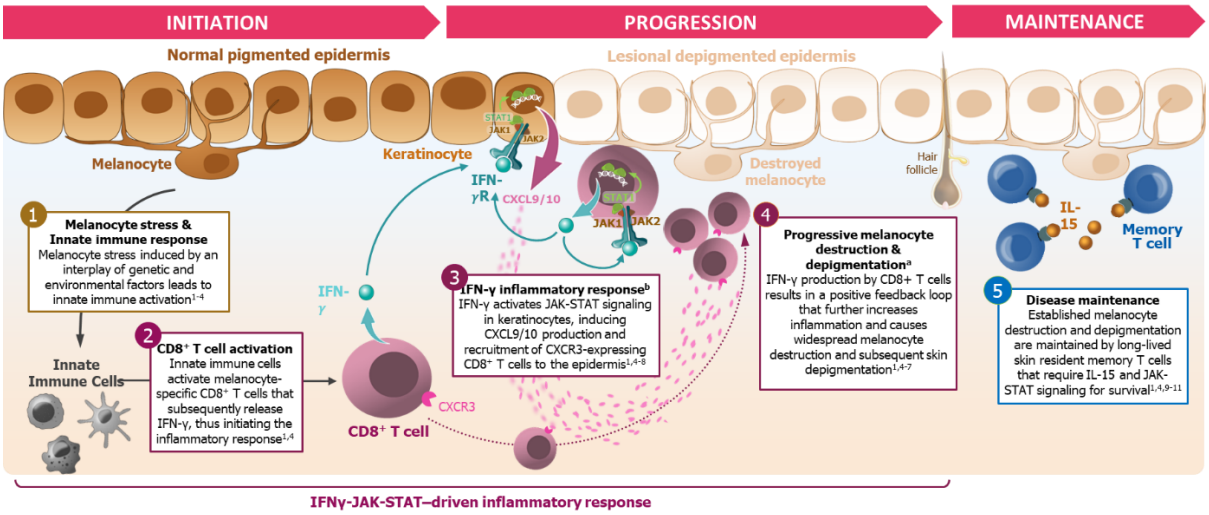
Pathogenesis of vitiligo

The pathogenesis of vitiligo involves intrinsic defects within melanocytes and autoimmunity that targets these cells. During melanin production, large amounts of protein are manufactured. This increases the risk of misfolding, an event that activates a

stress pathway within the cell called the unfolded protein response (8, 25). Further, protein production results in the creation of reactive oxygen species from the metabolism of mitochondrial energy. These two pathways are hyperactivated in the melanocytes of patients with vitiligo, suggesting that their cells are less able to tolerate the demands of melanin production than those from healthy individuals. Once melanocytes become stressed, they release inflammatory signals that activate intrinsic immunity, which may represent the initiating event in vitiligo (8, 25).

Atypical activation of immune cells in the skin of vitiligo patients, including the recruitment of autoreactive CD8+ T cells to melanocytes, is mediated by IFNγ through the IFNγ-induced, JAK1/JAK2 regulated, CXCL9 and CXCL10 signalling pathway. Vitiligo patients have higher numbers of cytotoxic CD8+ T cells in their blood and skin, and the degree of CD8+ cellular infiltration correlates with disease severity in vitiligo patients (8, 25). The concentrations of both CXCL9 and CXCL10 are increased in the skin and blood of patients with vitiligo compared with healthy controls, and in patients with active versus stable vitiligo; these factors have been validated as biomarkers of vitiligo activity (26). **Figure *1*** presents details of the pathogenesis of vitiligo (8).

Figure 1. Pathogenesis of vitiligo



Abbreviations: CXCL, chemokine ligand; CXCR, chemokine receptor type; IL-15, interleukin-15; IFN-γ, interferon-gamma; JAK, Janus kinase; STAT, signal transducer and activator of transcription proteins.
Source: Image sourced from the Vitiligo Medical Deck 2022 (Incyte, data on file) per the following citations: 1 (8); 2 (27); 3 (28); 4 (29); 5 (30); 6 (31); 7 (26); 8 (32); 9 (33); 10 (34); 11 (35).

Diagnosis of vitiligo

The diagnosis of vitiligo can be made in the primary care setting based on the appearance of non-scaly lesions with distinct margins and pigment loss (20, 23).

The clinical diagnosis of vitiligo, according to the British Association of Dermatologists (BAD), the European Dermatology Forum, and the American Academy of Dermatology, is based on (9, 36, 37):

- **Physical examination (with or without Wood's lamp)**
    - The use of a Wood's lamp, a hand-held ultraviolet (UV) irradiation device that emits ultraviolet A (UVA), eases the identification of areas of depigmentation not visible to the naked eye and points of focal melanocyte loss (20)
- **Clinical history**
- **Laboratory tests (i.e., thyroid function, autoantibodies)**
    - Due to the high prevalence of autoimmune thyroid disease in patients with vitiligo, the BAD recommends a blood test to check thyroid function (7). The European Dermatology Forum recommends additional tests for autoimmune antibodies in patients with a high risk of additional autoimmune disease, i.e., patient's history, family history, and/or laboratory parameters supporting this (7)
- **Biopsy of lesional and non-lesional skin**
    - In cases of atypical presentation, assessment by a dermatologist may be required. This could include punch biopsies from lesioned and normal skin (9). For differential diagnosis, tests, such as mycology for fungal infection or molecular biology to detect lymphoma cells, may be performed as needed to rule out other conditions (7)

The BAD published recent guidelines (2021); however, these guidelines focus on treatments and the management of patients with vitiligo and do not include diagnosis (7).

Owing to the noticeability of their vitiligo (5, 36), diagnosis may be easier with patients of darker skin type. Skin type is defined by the Fitzpatrick skin grading scale, which consists of six skin types classified according to sun reactivity (**Table 4**) (38, 39).

Table 4. Fitzpatrick skin types

Fitzpatrick scale	Skin type (unexposed skin)	Sunburn characteristics
I	White skin (sun-reactive)	Always burns, never tans
II	White skin (sun-reactive)	Always burns, minimal tan
III	White skin (sun-reactive)	Burns minimally, tans moderately and gradually
IV	White skin (sun-reactive)	Burns minimally, tans well
V	Brown skin	Rarely burns, tans deeply
VI	Black skin	Never burns, tans deeply

Source: Fitzpatrick, 1988; Roberts 2009 (38, 39).

Assessment of disease extent

There is currently no consensus on the methods to assess the extent of a patient's vitiligo (40, 41); however, BSA and Vitiligo Area Scoring Index (VASI) are commonly used in clinical trials and clinical practice.

Body surface area

A commonly used scale is BSA, for which the percentage of vitiligo involvement is determined by the palmar or handprint (palm plus 5 digits) method. Clinicians use the palmar method to assess skin disease extent as a percent of total BSA (42). The palmar method mimics the patient's hand size to determine vitiligo depigmented area to the nearest 0.1 % assuming (42):

- Handprint as 1% BSA (palm + 5 digits, with fingers tucked together & thumb tucked to the side)
- Thumbprint as 0.1% BSA

A cross-sectional study of the natural history of vitiligo suggests that nearly half of the vitiligo population (45.2%) have >5% BSA involvement (43). In the same study, patients with facial lesions were significantly more likely to have a higher extent of disease (>5% BSA) compared with patients with no facial lesions (63.2% vs 18.9%; $p < 0.05$) (43).

Vitiligo Area Scoring Index

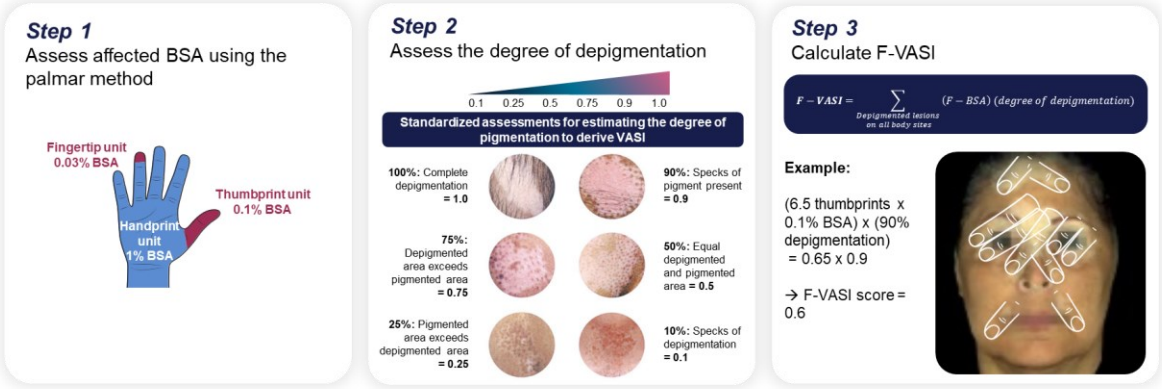
The VASI is a validated, sensitive, and quantitative approach for assessing the extent of depigmentation (42, 44). The extent of depigmentation measured using VASI may be determined for facial (F-VASI) (**Error! Reference source not found.**) (45) or total body vitiligo (T-VASI) (

Figure **3***) (45), both of which have been shown to exceed reliability expectations for measuring clinically meaningful change in vitiligo extent in RCTs (44, 46). F-VASI is calculated by multiplying F-BSA (i.e., affected areas on the face as a percentage of the total body area, measured using the palmar method) by the degree of depigmentation and has a maximum score of 3, denoting extensive depigmentation (*

Figure 2) (45), and can be calculated as follows (46):

$$F-VASI = \sum_{\substack{Depigmented\ lesions \\ on\ the\ face}} (F-BSA) * (degree\ of\ depigmentation)$$

Figure 2. Calculating F-VASI



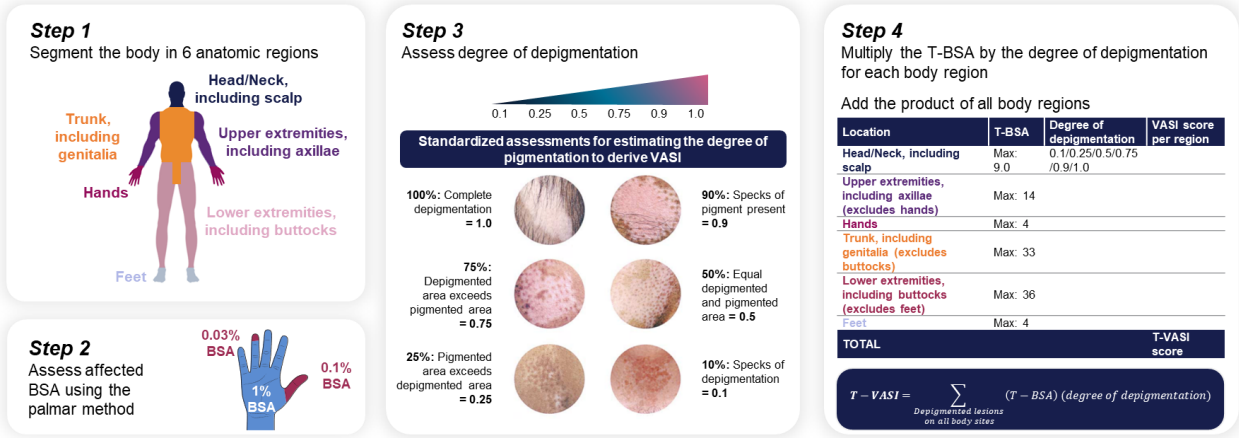
Abbreviations: BSA, body surface area; F-VASI, facial vitiligo area scoring index; T-BSA, total body surface areal T-VASI, total body vitiligo area scoring index; VASI, vitiligo area scoring index.
Source: Incyte. Medical deck - vitiligo VASI tools [Data on file] (45).

T-VASI is calculated by multiplying T-BSA (i.e., affected areas as a percentage of the total body area, measured using the palmar method) by the degree of depigmentation for the 6 segmented anatomic regions (head/neck/scalp, trunk/genitalia, upper extremities/axillae, lower extremities/buttocks, hands, and feet) (

Figure *3*) (45), as follows (46):

$$T-VASI = \sum_{\substack{Depigmented\ lesions \\ on\ all\ body}} (T-BSA) * (degree\ of\ depigmentation)$$

Figure 3. Calculating T-VASI



Abbreviations: BSA, body surface area; F-VASI, facial vitiligo area scoring index; T-BSA, total body surface areal T-VASI, total body vitiligo area scoring index; VASI, vitiligo area scoring index.
Source: Incyte. Medical deck - vitiligo VASI tools [Data on file] (45).

Results from psychometric analysis that was conducted to evaluate the psychometric properties of the F-VASI and T-VASI in adolescents and adults with NSV indicate that F-VASI and T-VASI instruments are reliable, valid, and responsive to change, with defined clinically meaningful within-patient change in adolescents and adults with NSV with depigmented areas ≤10% total BSA (facial and non-facial) with ≥0.5% facial BSA and ≥3% non-facial BSA (46, 47). The meaningful change threshold analysis revealed that an appropriate individual level threshold for identifying clinically relevant responders would be between 0.38 to 0.60 for F-VASI, and between 1.69 and 3.88 for T-VASI (46, 47).

B.1.3.1.1 Epidemiology

Incidence and prevalence

Vitiligo is the most common depigmenting skin disease (5). Around 65–95 million people worldwide are affected by vitiligo. The prevalence of diagnosed vitiligo is estimated between 0.2–0.8% in Europe, with geographic and methodologic differences (48, 49).

A recent UK-based analysis funded by Incyte using Clinical Practice Research Datalink (CPRD) estimated the prevalence of diagnosed vitiligo as 0.30% (0.21%−0.38%), and the

overall mean (range) incidence rate as 0.164 (0.096-0.188) per 1,000 person-years between 2010 and 2021 (50, 51). This reported prevalence of diagnosed vitiligo aligns with European estimates and is comparable to a recent UK analysis using the Optimum Patient Care Research Database (OPCRD), with a point prevalence of 0.3% (52).NSV constitutes 80% of the vitiligo population. (24).

B.1.3.1.2 Disease burden

Symptomatic burden

Vitiligo presents as lesions of depigmentation on the skin and hair depigmentation (whitening) in some cases where there are affected hair roots. It often begins with a pale patch on the skin that progressively turns completely white (5, 20). The edge of the depigmented patches may be smooth or irregular, red and inflamed or brownish in the case of hyperpigmentation. Discomfort to the skin, such as dryness, is not regularly reported, although occasionally affected areas may be itchy (6, 53, 54). Flares are often experienced during periods of stress, with two-thirds of patients (66.1%) surveyed in the Vitiligo And Life Impact Among International Communities (VALIANT) study reporting such flares, which are typically more frequent among patients with high BSA involvement (>5% BSA), darker skin types or facial lesions (43). Around two-thirds of patients experience itchiness before or during a flare-up of their symptoms (43).

The frequency of lesion locations varies; however, lesions commonly occur on the face, hands, and genitals. Studies on prevalence have reported facial vitiligo in 71–81% of study participants (24, 55). Specifically, among a cohort of patients with generalised vitiligo (n = 245), facial lesions were reported in 81.2% of patients. Other locations were: hands (71.4%); arms (60.8%); genitals (58.8%); legs (53.5%); chest/trunk (50.6%); feet (42.95%); back (36.3%); and neck (35.1%) (55). Facial involvement has a high impact on patients' global perception of the extent of vitiligo (56).

With NSV, children are particularly predisposed to facial vitiligo while the arm and forearm are the regions most likely to be affected in adults, i.e., those aged 18 to 30 years (57). Patients with early-onset vitiligo (<12 years of age) are more likely to present with lesions on the eyelid (21.0% vs 6.5%) and lower extremities (20.3% vs 3.7%) compared to

patients with later-onset vitiligo (>12 years of age) who more likely present with cases of upper extremities (16.3% vs 47.7%), particularly the hands (12.2% vs 40.2%) (58).

Autoimmune comorbidities

Around one-quarter of patients with vitiligo have at least one autoimmune comorbidity (59); however, the prevalence of autoimmune comorbidity with vitiligo varies between studies. In Europe, autoimmune comorbidities occurred in 15–42% of patients with vitiligo (60-62).

The primary autoimmune comorbidity among patients with vitiligo is thyroid disease/disorder; the BAD guidelines indicate that the incidence of thyroid disease is as high as 52% among patients with vitiligo, and that 3–90% of patients with vitiligo have antithyroid antibodies (7).

B.1.3.1.3 Humanistic burden

Psychosocial burden

Patients with vitiligo experience a significant burden on their quality of life (18, 63), especially if the depigmentation occurs on visible areas such as the face and hands (64-66). Vitiligo has a substantial psychological burden on patients (67-69), which can result in reduced productivity, the need for medication, and hospitalisation for mental health disorders (70-72).

In a study of the mental health burden in patients with vitiligo, Ramakrishna and colleagues reported that most patients (79%) had psychiatric morbidity (73). In the VALIANT study, more than half (54.2%) of patients in the UK reported symptoms of moderate-to-severe depression. Negative effects on daily activities are greater and rates of moderate-to-severe depression are higher in patients with a greater BSA affected, those with facial lesions, and those with a darker skin tone (74). Similarly, results from a large, population-based UK study demonstrate that people diagnosed with vitiligo have an increased risk of subsequently being diagnosed with new-onset depression (25%) and anxiety (23%) compared with the general population, and that this risk increase may be greatest in black and minority ethnic populations (up to 72% risk increase for recurrent depressive disorder). Results from the same study suggest that people with both vitiligo

and a mental health comorbidity have increased use of primary care services, and are twice as likely to have recorded time off work requests and unemployment (75).

The prevalence of psychosocial comorbidities is significantly higher among patients with vitiligo compared to healthy controls (71), with depression and anxiety being the most commonly reported psychosocial comorbidities (71). Patients with vitiligo are five times more likely to have depression than their peers who do not have vitiligo (76). In a hospital-based cross-sectional study, the severity of depression was higher in patients with vitiligo than in healthy controls, with a mean depression score (HAM-D) of 8.20 ± 3.99 versus 3.26 ± 1.91; depression was significantly associated with the impairment of HRQoL (77).

A large systematic literature review (SLR) (n = 161 studies) by Ezzedine and colleagues reported that the most commonly reported psychosocial comorbidities were depression (41 studies, 0.1–62.3%) and anxiety (20 studies, 1.9–67.9%). Other reported psychosocial comorbidities included feelings of stigmatisation (8 studies, 17.3–100%), adjustment disorders (12 studies, 4–93.9%), sleep disturbance (7 studies, 4.6–89.0%), relationship difficulties including sexual dysfunction (10 studies, 2.0–81.8%), and avoidance or restriction behaviour (9 studies 12.5–76%) (18). The prevalence of most psychosocial comorbidities was significantly higher than in healthy individuals (18). Furthermore, in an adult population diagnosed with vitiligo-representative UK primary care cohort (n = 9,994; to end of December 2020), 12.7% (n = 1,272) of patients had a pre-existing diagnosis of depression (the presence of one of more coded depression episodes), and 9.1% (n = 914) of patients had a diagnosis of anxiety (coded non-phobia related anxiety disorder) (52).

Suicidal thoughts

The literature on the association between vitiligo and attempted or completed suicide is sparse; however, suicidality was observed in 28% of patients in a study of psychiatric morbidity among patients with vitiligo (n = 53) (73). In a recent SLR of vitiligo cases (n = 12,043) compared with controls (n = 87,053,333), suicidal ideation was around seven times higher in patients with vitiligo (15.2% vs 2.0%; $p < 0.001$) (78). In addition, suicide attempts and suicide were also significantly higher in the vitiligo population compared with the control arm (3.2% vs 2.1%, $p < 0.001$) (79).

Stigmatisation

Patients living with vitiligo suffer stigmatisation as a result of the misconceptions associated with the disease. The misconceptions range from thoughts of the disease being contagious and caused by poor hygiene to causative links of superstitious external forces (18). The result of such stigmatisation is a feeling of self-consciousness and low self-esteem; particularly in children and adolescents who report regular stigmatisation (93.2%) and bullying (21.7%) due to their vitiligo, and resort to concealing the condition (80). Stigmatisation and associated bullying are of particular concern in children, leading to restricted activity and school attendance (6). In adults, stigmatisation results in social isolation and discrimination in employment, particularly in public-facing jobs (6). These conclusions are supported by the VALIANT study (n = 3,541 patients), where around half (49%) of patients with vitiligo reported feeling less confident or more self-conscious because of their disease and one-quarter (26.2%) considered the condition “a curse” (74).

B.1.3.1.4 Economic burden

Direct costs

Treatment-related costs

Several types of direct costs accrue from living with vitiligo. For the health service these include costs of primary care, outpatient care, and inpatient care (81). Treatment-related costs can be variable depending on the treatment.

A study reporting on phototherapy reported overall cost of treatment with UV therapy plus TCS was £813.38, while TCS alone was £599.98, and narrowband ultraviolet B (NB-UVB) was £774.64 (UK; 2017 costs; 9-month treatment phase), with dermatologist time being the key component of costs for both treatments (82).

Impact of mental health disorders

Costs associated with mental health disorders contribute to the overall direct costs for patients with vitiligo as the treatment of depression and anxiety is costly. A SLR of the global cost of depression, comparing patients with depression versus patients without depression, estimated the mean annual excess direct cost of depression in adults to be US$124–18,174. In the subgroup of patients who had depression as a comorbidity, the

cost was higher, at US$239–20,768 (83). The direct cost constitutes inpatient, outpatient, and emergency treatments as well as the cost of medication. No respective data from the UK or Europe was identified.

Indirect costs

The indirect costs of living with vitiligo comprise costs of lost productivity due to the disease and intangible costs related to reductions in quality of life (QoL) (81).

A UK study highlighted that the indirect cost of depression can vastly outweigh the direct cost of care. The study estimated that 109.7 million working days were lost in the year 2000 as a result of a diagnosis with depression (84). The total lost earnings were estimated to be £8 billion (84). Similarly, for the case of anxiety disorders, indirect costs account for the majority of the total costs, with morbidity costs being the primary cost (the loss resulting from a decline in the productivity of employees with anxiety disorders, i.e., absenteeism and presenteeism) and the loss resulting from the lack of employment of patients with anxiety disorders (i.e., unemployment cost) (85).

B.1.3.2 Clinical pathway of care

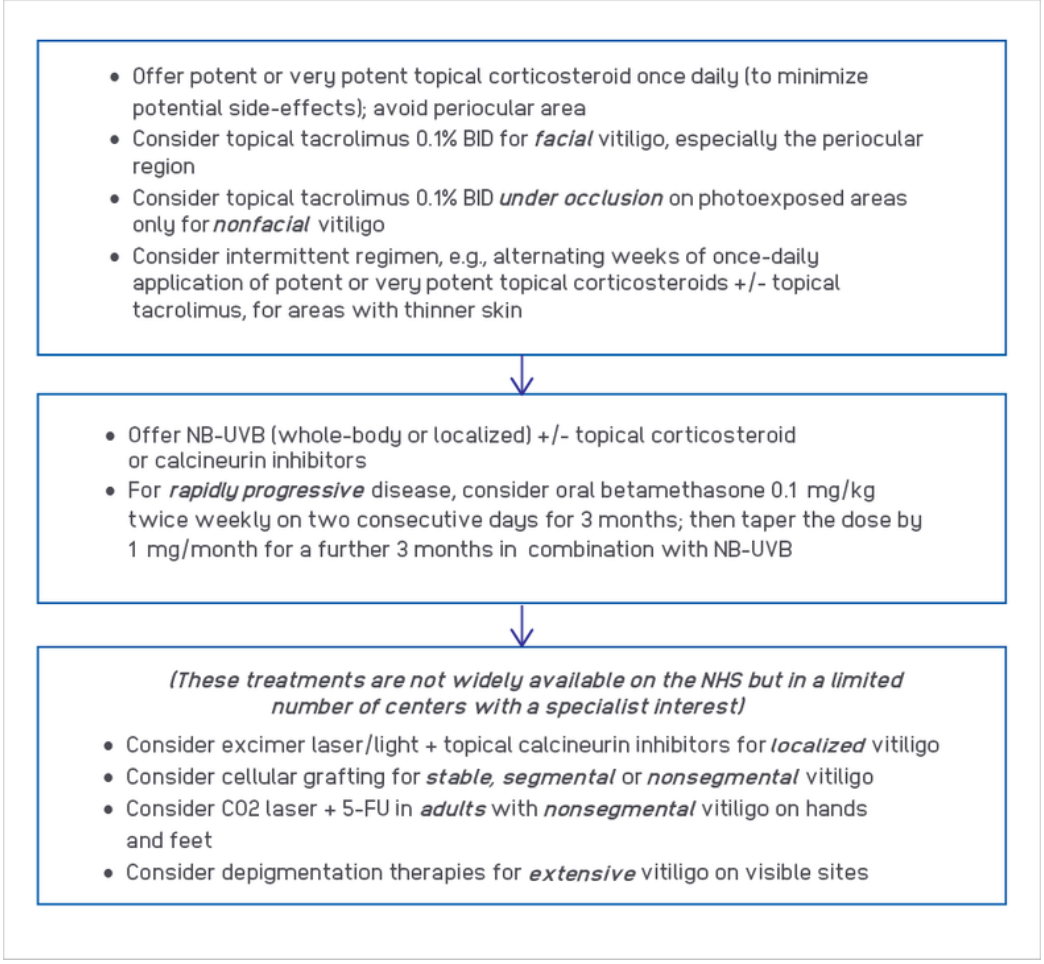
Guidelines for the management of patients with vitiligo are issued by the BAD and were last updated in 2021 (7). The guidelines place a strong emphasis on the general management of patients with vitiligo, including periodic evaluations of their HRQoL and recommending referral to psychological and other cognitive-behavioural services (**Figure 4**) (7).

The BAD guidelines consider only topical treatments for initial therapy (**Figure 4**) (7). TCS are recommended once daily for up to 2 months, with TCI as an option for facial and photo-exposed areas (7). To minimise the risk of side effects with the use of TCS, these could be recommended in alternating weeks with topical tacrolimus (7).

Patients whose disease is non-responsive to topical treatment and those with rapidly progressive disease are offered phototherapy or oral betamethasone, respectively, in addition to topical treatment (**Figure 4**) (7). Oral betamethasone is recommended for a maximum of 3 months; excimer laser in combination with TCI are considered for localised vitiligo, while surgical therapies are reserved for those with stable disease. CO2 laser in

combination with 5-fluorouracil are considered in adults with NSV on hands and feet, and depigmentation is considered for those with more extensive disease on visible areas (**Figure 4**) (7). None of the treatments in the BAD guidelines have a marketing authorisation for treatment of vitiligo in the UK.

Figure 4. BAD guidelines for the treatment of patients with vitiligo



Abbreviations: BAD, British Association of Dermatologists; BID, twice daily; CO2, carbon dioxide; FU, Fluorouracil; NB-UVB, narrowband ultraviolet B; NHS, National Health Service.

Source: Adapted from the BAD guidelines (Eleftheriadou et al., 2021) (7).

B.1.3.2.1 Current standard of care

The main treatment goals of vitiligo are to stop disease progression, induce repigmentation and prevent relapse, thus improving the patient's QoL and alleviating their psychosocial burden (7-9). Commonly prescribed treatments to achieve repigmentation include TCS, TCI, phototherapy, oral corticosteroids, antioxidants, and surgical techniques; however, none of these agents has been licensed for use in vitiligo, so their

use as repigmentation therapies is off-label (7-9). Further, antioxidants and surgical techniques are not available in the NHS.

B.1.3.2.2 Unmet need

The clinical course of vitiligo is chronic and unpredictable, with most patients experiencing alternating periods of pigment loss and stable disease over their lifetime (5). Due to the manifestation of the disease and its chronic, unpredictable course, vitiligo carries a high psychosocial burden on patients. An estimated 58.7% of patients with vitiligo internationally report having been diagnosed with a mental health disease, most commonly anxiety and depression disorders (74). In the UK, the most common mental health comorbidities are anxiety/depression (24.6%), depression (18.5%) and anxiety (16.0%) (50). In the first five years following diagnosis with vitiligo, over a quarter of patients (26.6%) use antidepressants and/or anxiolytics (51). In particular, children and adolescents report regular stigmatisation (93.2%) and bullying (21.7%) due to their vitiligo, resulting in low self-esteem, restricted activity and school attendance and social isolation (80). Additionally, those with darker skin tones, where vitiligo is more noticeable, are thought to report worse QoL (5). The NHS Long Term Plan states that mental health is a clinical priority, thus highlighting the urgent need to address the psychosocial burden resulting from vitiligo (86).

Patients with receiving treatment for vitiligo use off-label treatments such as TCS, TCI and phototherapy, which have well-known risks and limitations for their use in vitiligo, including limited evidence for efficacy and long-term safety (10, 11), low compliance (12, 13), and limited tolerability (9, 14-17). Additionally, access to phototherapy for patients with vitiligo in the NHS may add to the disease burden on patients.

As the first licensed treatment for NSV, ruxolitinib cream addresses an unmet need by offering a tolerable and effective treatment for what had been a chronically neglected and underserved patient population. Ruxolitinib cream halts depigmentation and enables re-pigmentation to natural skin colour via an anti-inflammatory mode of action that also facilitates endogenous repigmentation of lesions (87).

B.1.3.2.3 Positioning of ruxolitinib cream in the UK treatment pathway

Having received its marketing authorisation from MHRA in July 2023, ruxolitinib cream is currently the only approved treatment for vitiligo (5, 6).

Ruxolitinib cream is anticipated to be positioned as a step change option between the first and second line (7) for adults and adolescents from 12 years of age with NSV with facial involvement for whom the disease has not responded to TCS, TCI, or for whom TCS or TCI are contraindicated, not tolerated or otherwise medically inadvisable. Therefore, TCS, TCI and phototherapy are not relevant comparators. Notwithstanding, an assessment was conducted to also investigate the feasibility of deriving treatment effect estimates for ruxolitinib cream relative to TCS, TCI and phototherapy. The ITC FA found that there is an insufficient evidence base to robustly compare the efficacy of ruxolitinib cream to existing off-label therapies. Details of the ITC are presented in section B2.9 and in Appendix D.

This position is more relevant to the NHS clinical practice and reflects a position where ruxolitinib cream provides the most clinical benefit for patients with the highest unmet need in England and Wales.

B.1.4 Equality considerations

Although vitiligo is more noticeable and associated with a higher disease burden in people with darker skin tones, as noted in the draft scope, Incyte aims to make ruxolitinib cream available for all patients, including adolescent and adult patients from 12 years of age. Therefore, no equality issues are foreseen in terms of providing ruxolitinib cream to eligible patients.

Access to phototherapy for patients with vitiligo varies across regions in the country. Currently in the NHS, dermatology waiting lists vary between 12-24 months for general dermatology clinics (88). In addition, once seen in secondary care, many patients with vitiligo are unable to start phototherapy either due to long NHS waiting lists (over one year at some centres, following first assessment by a dermatologist) for this treatment option, and/or personal time constraints (i.e., the need to attend three times a week for 9-12 months) (88). Furthermore, many dermatology departments offer phototherapy to a small

cohort of patients with vitiligo due to the prolonged course of treatment (88). As such, patients with other dermatological diseases (such as eczema or psoriasis) who usually require shorter courses are prioritised instead (88).

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

A SLR was conducted to identify relevant clinical trial evidence for this submission (89). Full details of the process and methods used to identify the clinical evidence relevant to the technology being appraised are presented in Appendix D.

B.2.1.2 Non-randomised clinical effectiveness studies

There are no non-randomised clinical studies presented in this submission.

B.2.2 List of relevant clinical effectiveness evidence

The clinical effectiveness of ruxolitinib cream is evaluated using pooled data from the two pivotal studies: INCB 18424-306 (TRuE-V1 [NCT04052425]) (2) and INCB 18424-307 (TRuE-V2 [NCT04057573]) (3). These studies were designed to provide evidence for the marketing authorisation of ruxolitinib cream for treating NSV with facial involvement, along with data from INCB 18424-308 (TRuE-V LTE [NCT04530344]) (4), the withdrawal and treatment extension study enrolling eligible patients who have completed either TRuE-V1 or TRuE-V2 (pivotal trials) (**Table 5**).

Table 5. Clinical effectiveness evidence: TRuE-V studies (2-4, 90-92)

Study	TRuE-V1 (NCT04052425) and TRuE-V2 (NCT04057573) (2, 3, 90, 91, 93)	TRuE-V LTE (NCT04530344) (4, 92)
Study design	Two identically designed, multinational, Phase 3, double-blind, vehicle-controlled RCTs, conducted across 101 centres. Patients were randomly assigned in a 2:1 ratio to apply ruxolitinib cream or vehicle control twice daily for 24 weeks to all vitiligo areas on the face and body, after which all patients could apply ruxolitinib cream through week 52	Phase 3, double-blind, vehicle-controlled, randomised withdrawal and treatment extension study enrolling eligible patients who have completed either TRuE-V1 or TRuE-V2, and tolerated ruxolitinib cream without safety concerns and with good compliance for continuation. Eligible patients in this treatment extension study were assigned to one of 2 cohorts, Cohort A or Cohort B, based on their F-VASI responses at the time of enrolment in this extension study (i.e., at Week 52)
Population	Patients 12 years of age or older diagnosed with NSV with depigmentation covering 10% or less of total BSA, including at least 0.5% of BSA on the face and at least 3% of BSA on non-facial areas. Patients were also required to have F-VASI scores of 0.5 or higher and T-VASI scores of 3 or higher	Patients from the TRuE-V1 or TRuE-V2 studies conducted in adults and adolescents with vitiligo who adequately completed the visits and assessments required for the treatment periods, as defined in the TRuE-V1 or TRuE-V2 study protocols, and tolerated ruxolitinib cream without safety concern for continuation
Intervention(s)	Ruxolitinib cream	Ruxolitinib cream (Cohort A or B)
Comparator(s)	Vehicle cream	Vehicle cream (Cohort A)
Indicate if trial supports application for marketing authorisation	Yes	No
Rationale for use/non-use in the model	Confirmatory studies supporting the indication	Results of this LTE study inform long-term F-VASI75, the time to relapse following treatment discontinuation, and the time to regain F-VASI75 after relapse
Reported outcomes specified in the decision problem	**Repigmentation and cessation of spread:** • Proportion of patients achieving at least 50% improvement from baseline in F-VASI (F-VASI50), at least 75% improvement from baseline in F-VASI (F-VASI75) and at least 90% improvement from baseline in F-VASI (F-VASI90) at Week 24 • Proportion of patients achieving F-VASI75 and F-VASI90 at Week 52 • Proportion of patients achieving at least 50% improvement from baseline in T-VASI (T-VASI50) at Week 24 • Proportion of patients achieving T-VASI50 and 75% improvement from baseline in T-VASI (T-VASI75) at Week 52	• Time to relapse (defined as < F-VASI75) for participants randomised in Cohort A • Time to maintain F-VASI90 response (i.e., maintenance of F-VASI90 response) for participants randomised in Cohort A • Time to regain response (F-VAS75 and F-VASI90) for patients randomised in Cohort A who relapsed after entering the extension treatment period • Proportion of patients in Cohort A and Cohort B who achieve F-VASI50, F-VASI75 and F-VASI90 **Adverse effects of treatment**

	Global assessment of vitiligo: • Proportion of patients achieving a facial physician's global vitiligo assessment (F-PhGVA) or a total physician's global vitiligo assessment (T-PhGVA) of clear (0) or almost clear (1) during the treatment period (double-blind and treatment extension periods) **Cosmetic acceptability:** • Proportion of patients achieving a vitilito noticeability scale (VNS) of "4- a lot less noticeable" or "5-no longer noticeable" at week 24 **Health related quality of life:** • Change from baseline in dermatology life quality index (DLQI), vitiligo-specific quality-of-life instrument (VitiQoL) and HADS (hospital anxiety and depression scale) **Adverse effects of treatment**	

Abbreviations: BSA, body surface area; DLQI, dermatology life quality index; F-PhGVA, facial physician's global vitiligo assessment; F-VASI, facial vitiligo area scoring index; F-VASI 50/75/90, 50%/75%/90% improvement from baseline in face vitiligo area scoring index score; HADS, hospital anxiety and depression scale; NSV, non-segmental vitiligo; T-PhGVA, total physician's global vitiligo assessment; TRuE-V1, topical ruxolitinib evaluation in vitiligo study 1; TRuE-V2, topical ruxolitinib evaluation in vitiligo study 2; TRuE-V LTE, topical ruxolitinib evaluation in vitiligo long-term extension; T-VASI, total body vitiligo area scoring index; VitiQoL, vitiligo-specific quality-of-life instrument; VNS, vitiligo noticeability scale.
Source: INCB 18424-306 CSR (2, 90); INCB 18424-307 CSR (3, 91); INCB 18424-308 CSR (4, 92).

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

The ruxolitinib cream clinical development programme comprises three studies in patients with vitiligo (2-4, 90-92): two identically designed Phase 3 pivotal trials (TRuE-V1 and TRuE-V2) (2, 3, 90, 91, 93), and a Phase 3 open-label extension study (TRuE-V LTE) (4, 92) (see **Table 5**).

The two identically designed Phase 3, double-blind, 24-week confirmatory studies (TRuE-V1 and TRuE-V2) (2, 3, 93, 94) are the pivotal trials supporting the current submission. Pooled data from these two trials collected from randomisation through to the last patient visit are presented in this submission. In addition, this submission also includes long-term efficacy and safety results from the TRuE-V LTE Phase 3, vehicle controlled, double-blind, randomised withdrawal (Cohort A) and open-label treatment- extension- (Cohort B) study, which enrolled eligible patients who completed the TRuE-V1 or TRuE-V2 studies (4, 92).

Table 6 provides a comparative summary of trial methodology of the three studies in patients with vitiligo (90-92).

Table 6. Comparative summary of trial methodology (90-92)

Study	TRuE-V1 (NCT04052425) (90) and TRuE-V2 (NCT04057573) (91)	TRuE-V LTE (NCT04530344) (92)
Trial design	Phase 3, double-blind, randomised, vehicle-controlled, efficacy and safety study of ruxolitinib cream over 24 weeks followed by an open-label extension period of 28 weeks in patients with vitiligo; double blind period over 24 weeks followed by an open-label extension up to 52 weeks. Patients, who were stratified according to geographic region (North America or Europe) and Fitzpatrick skin type (I [pale white] or II [white] vs. III [light brown] to VI [deeply pigmented dark brown to black]), were randomly assigned in a 2:1 ratio to apply ruxolitinib cream or matching vehicle cream to all depigmented vitiligo lesions on the face and body identified at trial entry for 24 weeks. Patients and investigators remained unaware of the trial-group assignments throughout the trials; the sponsor was aware of the trial-group assignments after database lock for the primary analysis. After completion of the Week 24 visit, all the patients could apply ruxolitinib cream for an additional 28 weeks in an open-label treatment extension phase of the trials.	Phase-3, double-blind, vehicle-controlled, randomised withdrawal (Cohort A) and treatment extension (Cohort A and Cohort B) study to assess the long-term efficacy and safety of ruxolitinib cream in patients with vitiligo. Eligible participants in this study were assigned to 1 of 2 cohorts, Cohort A or Cohort B, based on their F-VASI responses at the time of enrolment in this study (i.e., at Week 52). Treatment in Cohort A is a randomised withdrawal design and provided data on the duration of response following withdrawal of ruxolitinib cream and maintenance of response with its continued use. Participants who achieved complete or almost complete facial repigmentation (i.e., achieve ≥ F-VASI90) at Week 52 in the parent study were assigned to Cohort A and stratified by the original treatment received on study Day 1 of the parent study and randomised 1:1 to treatment with vehicle cream or ruxolitinib cream for an additional 52 weeks (i.e., until end of treatment [EOT] at Week 104). However, any participants in Cohort A who experienced relapse (defined as < F-VASI75) received ruxolitinib cream as an open-label rescue treatment until they completed treatment (Week 104 or EOT). Treatment in Cohort B provided long-term efficacy and safety data for ruxolitinib cream in vitiligo patients. Participants who did not achieve ≥ F-VASI90 at Week 52 of the parent studies were assigned to Cohort B and continued ruxolitinib cream for 52 weeks (i.e., until EOT Week 104). For Cohort A, the participant, investigator, and sponsor remained blinded to treatment assignment; the treatment for Cohort B was open-label.
Eligibility criteria for patients	**Inclusion criteria** • Adolescents and adults aged ≥ 12 years • Patients with a clinical diagnosis of NSV with depigmented area including ≥ 0.5% BSA on the face, ≥ 0.5 F-VASI, ≥ 3% BSA on non-facial areas, ≥ 3 T-VASI, and total body vitiligo area (facial and non-facial) not exceeding 10% BSA • Patients who agreed to discontinue all agents used to treat vitiligo from screening through the final safety follow-up visit. Over-the-counter preparations deemed acceptable by the investigator and camouflage makeups were permitted. • Male and female patients must have been willing to take appropriate contraceptive measures to avoid pregnancy or fathering a child for the duration of study participation with the exception of the following: o Females of non-childbearing potential o Prepubescent adolescents **Exclusion criteria** • Patients who had no pigmented hair within any of the vitiligo areas on the face • Other forms of vitiligo (e.g., segmental) or other differential diagnosis of vitiligo or other skin depigmentation disorders (e.g., piebaldism, pityriasis alba, leprosy, postinflammatory hypopigmentation, progressive macule hypomelanosis, nevus anemicus, chemical leukoderma, and tinea versicolor) • Patients who had used depigmentation treatments (e.g., monobenzone) for past treatment of vitiligo or other pigmented areas. Prior use of hydroquinone was not prohibited (as it is a bleaching agent, not a depigmentation treatment) • Patients with concurrent conditions and history of other diseases:	**Inclusion criteria** • Enrolled and receiving treatment in either TRuE-V1 or TRuE-V2 • Currently tolerating ruxolitinib cream in the parent study and no safety concerns per investigators judgment • Has demonstrated compliance, as assessed by the investigator, with the parent study protocol requirements • Willingness and ability to comply with scheduled visits, treatment plans, and any other study procedures indicated in this protocol. • Male and female patients must be willing to take appropriate contraceptive measures to avoid pregnancy or fathering a child for the duration of study participation, with the exception of the following: a) Females of non-childbearing potential b) Prepubescent adolescents (age 12-18 years old at the time enrolled in parent studies). • For adult patient, ability to comprehend and willingness to sign an informed consent form (ICF); for adolescent patient, written informed consent of the parent(s) or legal guardian and written assent from the adolescent patient when possible* **Exclusion criteria** • Has been permanently discontinued from study treatment in the parent study for any reason. • Patients with an uncontrolled intercurrent illness or any concurrent condition

Study	TRuE-V1 (NCT04052425) (90) and TRuE-V2 (NCT04057573) (91)	TRuE-V LTE (NCT04530344) (92)
	• Any other skin disease that, in the opinion of the investigator, would interfere with the study medication application or study assessments • Active acute bacterial, fungal, or viral skin infection (e.g., herpes simplex, herpes zoster, chicken pox) within 1 week before baseline • Conditions at baseline that would interfere with evaluation of vitiligo • Any serious illness or medical, physical, or psychiatric condition(s) that, in the investigator's opinion, would interfere with full participation in the study, including administration of study drug and attending required study visits; pose a significant risk to the patient; or interfere with interpretation of study data. Examples include but are not limited to the following: o Clinically significant or uncontrolled cardiac disease, including unstable angina, acute myocardial infarction within six months from Day one of study drug administration, New York Heart Association Class III or IV congestive heart failure, and arrhythmia requiring therapy or uncontrolled hypertension (blood pressure > 150/90 mmHg) unless approved by the medical monitor/sponsor o History of thrombosis, including deep venous thrombosis and pulmonary embolism o Patients with concurrent malignant disease or a history of that in the five years preceding the baseline visit except for adequately treated nonmetastatic malignancies o Current and/or history of liver disease, including known hepatitis B or C, with hepatic or biliary abnormalities o History of alcoholism or drug addiction within one year before screening or current alcohol or drug use that, in the opinion of the investigator, will interfere with the patient's ability to comply with the administration schedule and study assessments o Patients who are committed to an institution by virtue of an order issued either by the judicial or the administrative authorities • Patients using any of the following treatments within the indicated washout period before baseline: • One week: Topical drugs when used on the vitiligo areas, for example, corticosteroids, calcineurin, and phosphodiesterase type 4 inhibitors or retinoids • Four weeks: o Melanocyte-stimulating agents (e.g., afamelanotide) o Immunomodulating systemic medications (e.g., corticosteroids, methotrexate, cyclosporine) o Any other systemic therapies that could increase the skin sensitivity to UV / visible light or impact skin pigmentation, for example, tetracyclines, metoxypsoralens o Received live vaccine. Live vaccine is prohibited during the course of the study and within four weeks after the EOT visit • Eight weeks: Laser or any kind of phototherapy, including tanning bed or	that, in the investigator's opinion, would jeopardise the safety of the patient or compliance with the Protocol. • Pregnant or breastfeeding woman. • Patients who live with anyone participating in any current Incyte-sponsored ruxolitinib cream study

Study	TRuE-V1 (NCT04052425) (90) and TRuE-V2 (NCT04057573) (91)	TRuE-V LTE (NCT04530344) (92)
	intentional UV exposure • Five half-lives or 12 weeks, whichever is longer: Biologic agents, investigational or experimental therapy or procedures for vitiligo. Investigational biologics should be discussed with the sponsor to determine whether a longer period of discontinuation is required • Patients who have previously received JAK inhibitors, systemic or topical • Patients with clinically significant abnormal laboratory values at screening: • Haemoglobin (< 10 g/dL) • Liver function tests: o Aspartate transaminase (AST) or alanine aminotransferase (ALT) ≥ 2 × upper limit normal (ULN) o Alkaline phosphatase and/or bilirubin > 1.5 × ULN (isolated bilirubin > 1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%) • Severe renal disease (with creatinine clearance < 30 ml/min) or renal disease requiring dialysis • Clinically significant abnormal thyroid-stimulating hormone (TSH) or free thyroxine (T4) at screening as determined by the investigator • Positive serology test results at screening for human immunodeficiency virus (HIV) antibody • Body mass index (BMI) < 17 or > 40 kg/m2. • Pregnant or lactating patients, or those considering pregnancy during the period of their study participation • Patients who, in the opinion of the investigator, are unable or unlikely to comply with the administration schedule and study evaluations • Employees of the sponsor or investigator or are otherwise dependents of them	
Settings and locations where the data were collected	TRuE-V1: This trial was conducted at 45 study centres in North America (United States and Canada) and Europe (Bulgaria, France, Germany, Italy, the Netherlands, Poland, and Spain). TRuE-V2: This trial was conducted at 49 study centres in North America (United States and Canada) and Europe (Bulgaria, France, Germany, Italy, the Netherlands, Poland, and Spain).	TRuE-V1: This trial was conducted at 45 study centres in North America (United States and Canada) and Europe (Bulgaria, France, Germany, Italy, the Netherlands, Poland, and Spain). TRuE-V2: This trial was conducted at 49 study centres in North America (United States and Canada) and Europe (Bulgaria, France, Germany, Italy, the Netherlands, Poland, and Spain).
Trial drugs	**Intervention** • Ruxolitinib cream, for 24 weeks **Comparator** • Vehicle cream	**Intervention** • Cohort A: Patients were randomised 1:1 to receive ruxolitinib cream and vehicle cream • Cohort B: Patients continued to receive ruxolitinib cream
Primary outcomes	• Proportion of patients achieving F-VASI75 response: Decrease (improvement) of at least 75% from baseline in the facial Vitiligo Area Scoring Index (F-VASI; range, 0 to 3, with higher scores indicating a greater area of facial depigmentation) at Week 24	• Time to relapse, defined as < F-VASI75, for patients who are randomised in Cohort A
Secondary outcomes (including scoring methods	• Proportion of patients achieving F-VASI50 response: Decrease (improvement) of at least 50% from baseline in the facial vitiligo area scoring index (F-VASI; range, 0	• Time to maintain ≥ F-VASI90 response, for patients who are randomised in cohort A

Study	TRuE-V1 (NCT04052425) (90) and TRuE-V2 (NCT04057573) (91)	TRuE-V LTE (NCT04530344) (92)
and timings of assessments)	to 3, with higher scores indicating a greater area of facial depigmentation) at Week 24 and Week 52 • Proportion of patients achieving F-VASI75 response: Decrease (improvement) of at least 75% from baseline in the facial vitiligo area scoring index (F-VASI; range, 0 to 3, with higher scores indicating a greater area of facial depigmentation) at Week 24 and Week 52 • Proportion of patients achieving F-VASI90 response: Decrease (improvement) of at least 90% from baseline in the facial vitiligo area scoring index (F-VASI; range, 0 to 3, with higher scores indicating a greater area of facial depigmentation) at Week 24 and Week 52 • Proportion of patients achieving T-VASI50 response: Achieving at least 50% improvement from baseline in T-VASI at Week 24 and Week 52 • Proportion of patients achieving T-VASI75 response: Achieving at least 75% improvement from baseline in T-VASI at Week 24 and Week 52 • VNS 4/5: Proportion of patients achieving a VNS of "4 – A lot less noticeable" or "5 – No longer noticeable" at Week 24 and Week 52	• Proportion of patients who achieve F-VASI50, F-VASI75 and F-VASI90 during the extension treatment period • Actual measurements, change, and percentage change from baseline in F-VASI. • Proportion of patients who achieve T-VASI50, T-VASI75 and T-VASI90 during the extension treatment period. • Actual measurements, change, and percentage change from baseline in T-VASI • Actual measurements, change, and percentage change from baseline in F-BSA • Actual measurements, change, and percentage change from baseline in T-BSA. • Proportion of patients achieving a VNS of "4 – A lot less noticeable" or "5 – No longer noticeable" during the extension treatment period • Time to regain ≥ F-VASI90 in patients who relapsed after entering extension treatment period • Time to regain ≥ F-VASI75 in patients who relapsed after entering extension treatment period
Safety	The frequency and severity of adverse events	The frequency and severity of adverse events
Exploratory endpoints	• Proportion of participants achieving an F-PhGVA of clear (0) or almost clear (1) during the treatment period (double-blind and treatment extension periods) • Proportion of participants achieving a T-PhGVA of clear (0) or almost clear (1) during the treatment period (double-blind and treatment extension periods) • Change from baseline in DLQI (or CDLQI) during the treatment period (double-blind and treatment extension periods) • Change from baseline in VitiQoL during the treatment period (double-blind and treatment extension periods) • Change from baseline in HADS during the treatment period (double-blind and treatment extension periods)	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate transaminase; ; BSA, body surface area; CDLQI; children dermatology life quality index; DLQI, dermatology life quality index; EOT, end of treatment; F-BSA, facial body surface area; F-PhGVA, facial physician's global vitiligo assessment; F-VASI 50/75/90, achieving at least 50%/75%/90% improvement from baseline in face vitiligo area scoring index score; HADS, hospital anxiety and depression scale; HIV, human immunodeficiency virus; ICF, informed consent form; JAK, janus kinase; T4, thyroxine; T-BSA; T-PhGVA; T-PhGVA, total physician's global vitiligo assessment; TRuE-V1, topical ruxolitinib evaluation in vitiligo study 1; TRuE-V2, topical ruxolitinib evaluation in vitiligo study 2; TRuE-V LTE, topical ruxolitinib evaluation in vitiligo long-term extension; TSH, thyroid-stimulating hormone; T-VASI50/75, achieving at least 50%/75% improvement from baseline in total body vitiligo area scoring index; ULN, upper limit normal; UV, ultraviolet; VitiQoL, vitiligo-specific quality-of-life instrument; VNS, vitiligo noticeability scale.
*Adolescents, who during the course of the study become legal adults, will be asked for their consent to continue the study, and in the event of lack thereof, will be discontinued from further participation.
Source: INCB 18424-306 (TRuE-V1) protocol (90), INCB 18424-307 (TRuE-V2) protocol (91), and INCB 18424-308 (TRuE-V LTE) protocol (92).

B.2.3.1 TRuE-V1 (NCT04052425) and TRuE-V2 (NCT04057573)

TRuE-V1 and TRuE-V2 are two identically designed Phase 3 studies composed of double-blind vehicle-controlled and open-label treatment-extension periods lasting 24 and 28 weeks, respectively, that were conducted to evaluate the efficacy and safety of ruxolitinib cream in patients with vitiligo (2, 3, 90, 91, 93).

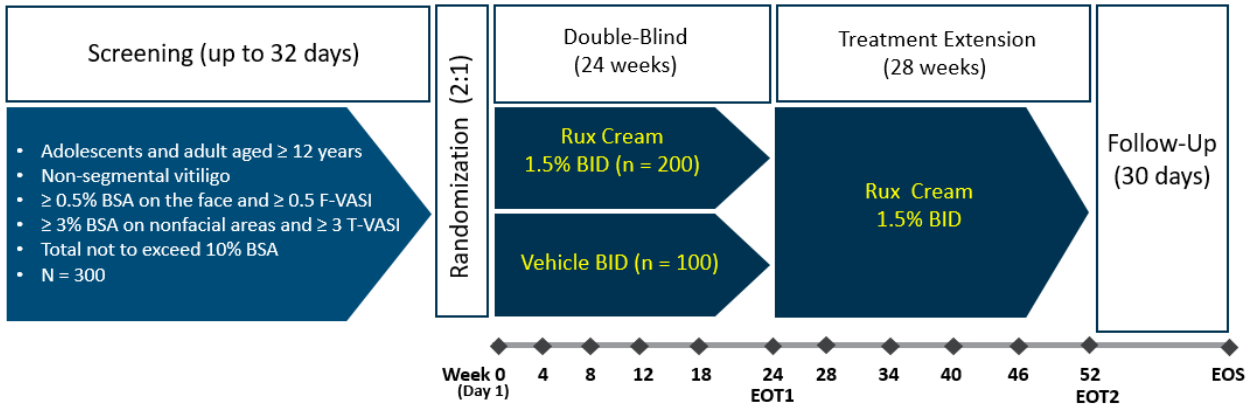
An interactive response technology system was used to manage enrolment, including assignment of patient trial numbers, tracking of visits, randomisation according to prespecified characteristics, masking of trial-group assignments, and management of trial-drug inventory (2, 3, 90, 91, 93).

Patients were stratified according to (2, 3, 90, 91, 93):

- Geographic region (North America or Europe), and
- Fitzpatrick skin type (I [pale white] or II [white] vs. III [light brown] to VI [deeply pigmented dark brown to black])

The trial design is illustrated in **Figure 5**. Following a screening period lasting up to 32 days, patients were randomly assigned in a 2:1 ratio to apply ruxolitinib cream or vehicle control for 24 weeks to all vitiligo areas on the face and body. After completion of the week 24 visit, all the patients were allowed to switch to ruxolitinib cream for an additional 28 weeks in an open-label treatment extension phase of the trials (2, 3, 90, 91, 93). Patients and investigators remained unaware of the trial-group assignments throughout the trials; the sponsor was aware of the trial-group assignments after database lock for the primary analysis (2, 3, 90, 91, 93).

Figure 5. Study design schema for TRuE-V1 and TRuE-V2 (90, 91)



Abbreviation: BSA, body surface area; F-VASI, Face Vitiligo Area Scoring Index; F-VASI50, achieving at least 50% improvement from baseline in face vitiligo area scoring index score; F-VASI75, achieving at least 75% improvement from baseline in face vitiligo area scoring index score; F-VASI90, achieving at least 90% improvement from baseline in face vitiligo area scoring index score; Rux, ruxolitinib cream; TRuE-V1, topical ruxolitinib evaluation in vitiligo study 1; TRuE-V2, topical ruxolitinib evaluation in vitiligo study 2; T-VASI, total body Vitiligo Area Scoring Index; T-VASI50, achieving at least 50% improvement from baseline in total body vitiligo area scoring index; VNS 4 or 5, vitiligo noticeability score of 4 or 5.
Source: INCB 18424 306 CSR and INCB 18424 307 CSR (2, 3).

Demographics and baseline characteristics

Demographics of all patients in the ITT population were generally well balanced -across the treatment groups, and there were no meaningful differences in the demographic characteristics of the study populations between studies (see **Table 7**) (95). In TRuE-V1, patients were mostly adults (89.1%) with a higher proportion of female patients (56.4%) and a mean age of 40.2 years (SD: 15.85 years). The majority of patients had Fitzpatrick Skin Type III, IV, V, or VI (61.5%). A higher proportion of patients in the ruxolitinib cream group were female (61.5%) than in the vehicle cream treatment group (45.9%) (2). In TRuE-V2, patients were mostly adults (89.5%) with an approximately even sex distribution and a mean age of 39.0 years (SD: 14.30 years). The majority of patients had Fitzpatrick Skin Type III, IV, V, or VI (73.2%). As planned, at least 10% of patients in each study were adolescents (3). Participants (n = 13) from study site 710 in TRuE-V2 were excluded from the study due to non-compliance with the protocol and concerns with data quality (94). In the pooled population, demographics of all patients in the ITT population were generally well balanced- across the treatment groups (2, 3).

Table 7. Summary of demographic characteristics (ITT Population) (93, 95)

Variable	TRuE-V1			TRuE-V2			Pooled Population		
	Vehicle cream (N = 109)	Ruxolitinib cream (N = 221)	Total (N = 330)	Vehicle cream (N = 115)	Ruxolitinib cream (N = 229)	Total (N = 344)	Vehicle cream (N = 224)	Ruxolitinib cream (N = 450)	Total (N = 674)
Age (years)									
n	109	221	330	115	229	344	224	450	674
Mean (SD)	39.7 (16.71)	40.5 (15.44)	40.2 (15.85)	39.8 (12.12)	38.6 (15.29)	39.0 (14.30)	39.7 (14.50)	39.5 (15.38)	39.6 (15.08)
Median	38.0	40.0	39.0	39.0	38.0	38.0	39.0	39.0	39.0
Min, max	12, 79	12, 79	12, 79	13, 68	12, 77	12, 77	12, 79	12, 79	12, 79
Age group, n (%)									
12 to 17 years	11 (10.1)	25 (11.3)	36 (10.9)	6 (5.2)	30 (13.1)	36 (10.5)	17 (7.6)	55 (12.2)	72 (10.7)
18 to 64 years	85 (78.0)	180 (81.4)	265 (80.3)	106 (92.2)	186 (81.2)	292 (84.9)	191 (85.3)	366 (81.3)	557 (82.6)
≥ 65 years	13 (11.9)	16 (7.2)	29 (8.8)	3 (2.6)	13 (5.7)	16 (4.7)	16 (7.1)	29 (6.4)	45 (6.7)
≤ 40 years	63 (57.8)	117 (52.9)	180 (54.5)	64 (55.7)	132 (57.6)	196 (57.0)	127 (56.7)	249 (55.3)	376 (55.8)
> 40 years	46 (42.2)	104 (47.1)	150 (45.5)	51 (44.3)	97 (42.4)	148 (43.0)	97 (43.3)	201 (44.7)	298 (44.2)
Sex, n (%)									
Male	59 (54.1)	85 (38.5)	144 (43.6)	55 (47.8)	117 (51.1)	172 (50.0)	114 (50.9)	202 (44.9)	316 (46.9)
Female	50 (45.9)	136 (61.5)	186 (56.4)	60 (52.2)	112 (48.9)	172 (50.0)	110 (49.1)	248 (55.1)	358 (53.1)
Fitzpatrick skin type, n (%)[a]									
I	3 (2.8)	10 (4.5)	13 (3.9)	1 (0.9)	2 (0.9)	3 (0.9)	4 (1.8)	12 (2.7)	16 (2.4)
II	40 (36.7)	74 (33.5)	114 (34.5)	32 (27.8)	57 (24.9)	89 (25.9)	72 (32.1)	131 (29.1)	203 (30.1)
III	43 (39.4)	89 (40.3)	132 (40.0)	45 (39.1)	90 (39.3)	135 (39.2)	88 (39.3)	179 (39.8)	267 (39.6)
IV	15 (13.8)	34 (15.4)	49 (14.8)	25 (21.7)	55 (24.0)	80 (23.3)	40 (17.9)	89 (19.8)	129 (19.1)
V	7 (6.4)	11 (5.0)	18 (5.5)	10 (8.7)	17 (7.4)	27 (7.8)	17 (7.6)	28 (6.2)	45 (6.7)
VI	1 (0.9)	3 (1.4)	4 (1.2)	2 (1.7)	8 (3.5)	10 (2.9)	3 (1.3)	11 (2.4)	14 (2.1)
Race, n (%)									
White	96 (88.1)	180 (81.4)	276 (83.6)	93 (80.9)	183 (79.9)	276 (80.2)	189 (84.4)	363 (80.7)	552 (81.9)
Black/African American	4 (3.7)	11 (5.0)	15 (4.5)	5 (4.3)	12 (5.2)	17 (4.9)	9 (4.0)	23 (5.1)	32 (4.7)
Asian	4 (3.7)	5 (2.3)	9 (2.7)	7 (6.1)	12 (5.2)	19 (5.5)	11 (4.9)	17 (3.8)	28 (4.2)

Variable	TRuE-V1			TRuE-V2			Pooled Population		
	Vehicle cream (N = 109)	Ruxolitinib cream (N = 221)	Total (N = 330)	Vehicle cream (N = 115)	Ruxolitinib cream (N = 229)	Total (N = 344)	Vehicle cream (N = 224)	Ruxolitinib cream (N = 450)	Total (N = 674)
American Indian/Alaska Native	0	1 (0.5)	1 (0.3)	0	1 (0.4)	1 (0.3)	0	2 (0.4)	2 (0.3)
Native Hawaiian/Pacific Islander	0	0	0	0	2 (0.9)	2 (0.6)	0	2 (0.4)	2 (0.3)
Not reported	3 (2.8)	16 (7.2)	19 (5.8)	3 (2.6)	3 (1.3)	6 (1.7)	6 (2.7)	19 (4.2)	25 (3.7)
Other	2 (1.8)	8 (3.6)	10 (3.0)	7 (6.1)	16 (7.0)	23 (6.7)	9 (4.0)	24 (5.3)	33 (4.9)
Ethnicity, n (%)									
Hispanic or Latino	20 (18.3)	53 (24.0)	73 (22.1)	32 (27.8)	50 (21.8)	82 (23.8)	52 (23.2)	103 (22.9)	155 (23.0)
Not Hispanic or Latino	86 (78.9)	151 (68.3)	237 (71.8)	80 (69.6)	175 (76.4)	255 (74.1)	166 (74.1)	326 (72.4)	492 (73.0)
Not reported	3 (2.8)	15 (6.8)	18 (5.5)	3 (2.6)	2 (0.9)	5 (1.5)	6 (2.7)	17 (3.8)	23 (3.4)
Unknown	0	1 (0.5)	1 (0.3)	0	0	0	0	1 (0.2)	1 (0.1)
Other	0	1 (0.5)	1 (0.3)	0	2 (0.9)	2 (0.6)	0	3 (0.7)	3 (0.4)
Region, n (%)									
North America	73 (67.0)	147 (66.5)	220 (66.7)	83 (72.2)	161 (70.3)	244 (70.9)	156 (69.6)	308 (68.4)	464 (68.8)
Europe	36 (33.0)	74 (33.5)	110 (33.3)	32 (27.8)	68 (29.7)	100 (29.1)	68 (30.4)	142 (31.6)	210 (31.2)
BMI (kg/m^2)									
Mean (SD)	26.13 (4.961)	26.60 (5.159)	26.44 (5.091)	27.14 (4.978)	26.75 (5.361)	26.88 (5.232)	26.65 (4.985)	26.68 (5.257)	26.67 (5.164)
Median	25.65	26.53	26.08	26.61	26.04	26.25	26.14	26.21	26.18
Min, max	17.2, 39.9	17.0, 54.2	17.0, 54.2	17.4, 39.1	17.0, 46.0	17.0, 46.0	17.2, 39.9	17.0, 54.2	17.0, 54.2

Error! Reference source not found. Type I: always burns, never tans (pale peach; blond or red hair; blue eyes; freckles).
Type II: usually burns, tans minimally (peach, fair; blond or red hair; blue, green, or hazel eyes).
Type III: sometimes mild burn, tans uniformly (light brown; fair with any hair or eye color).
Type IV: burns minimally, always tans well (moderate brown).
Type V: very rarely burns, tans very easily (dark brown).
Type VI: never burns, always tans (deeply pigmented dark brown to darkest brown).
Note: Participants from study site 710 in the TRuE-V2 study are included in the summary of demographic characteristics.
Abbreviations: ITT, intention to treat; SD, standard deviation; TRuE-V1, topical ruxolitinib evaluation in vitiligo study 1; TRuE-V2, topical ruxolitinib evaluation in vitiligo study 2.
Source: Summary of clinical efficacy. EMA submission (section 2.7.3) (95); Rosmarin et al, 2022 (93).

Treatment groups were generally well-balanced in terms of extent of disease at baseline, and there were no meaningful differences in baseline disease characteristics between studies (2, 3).

For the majority of patients (67.9% and 59.6% for TRuE-V1 and TRuE-V2, respectively), vitiligo was diagnosed in adulthood; the mean time since diagnosis was 13.63 years and 15.90 years before study entry for TRuE-V1 and TRuE-V2, respectively (see **Table 8)** (2, 3). In both studies, the majority of patients (74.2% and 73.8% for TRuE-V1 and TRuE-V2, respectively) had stable disease. Baseline F-VASI score ranged from 0.40 to 3.00 with a median of 0.70 for TRuE-V1 and from 0.45 to 3.00 with a median of 0.69 for TRuE-V2. The majority of patients (78.2% and 83.7% for TRuE-V1 and TRuE-V2, respectively) had an F-BSA involvement < 1.5%. Baseline T-VASI score ranged from 3.01 to 10.00 with a median of 6.34 for TRuE-V1 and from 2.65 to 10.00 with a median of 7.30 for TRuE-V2. The T-BSA involved at baseline ranged from 3.2% to 10.0% with a median of 7.60% for TRuE-V1 and from 3.50% to 10.10% with a median of 8.00% for TRuE-V2. These baseline disease characteristics are consistent with those of a patient population with vitiligo amenable to topical treatment (2, 3).

Table 8. Summary of baseline disease characteristics (ITT Population) (94, 95)

Variable	TRuE-V1			TRuE-V2			Pooled Population		
	Vehicle cream (N = 109)	Ruxolitinib cream (N = 221)	Total (N = 330)	Vehicle cream (N = 115)	Ruxolitinib cream (N = 229)	Total (N = 344)	Vehicle cream (N = 224)	Ruxolitinib cream (N = 450)	Total (N = 674)
Years since initial diagnosis of vitiligo									
Mean (SD)	13.18 (10.042)	13.85 (11.664)	13.63 (11.143)	16.01 (11.632)	15.84 (12.118)	15.90 (11.941)	14.63 (10.955)	14.86 (11.926)	14.79 (11.604)
Median	11.96	10.60	11.08	13.97	12.95	12.99	12.11	11.76	11.97
Min, max	0.1, 47.5	0.0, 60.5	0.0, 60.5	0.0, 59.5	0.0, 50.3	0.0, 59.5	0.0, 59.5	0.0, 60.5	0.0, 60.5
Vitiligo diagnosed in childhood, n (%)									
No	75 (68.8)	149 (67.4)	224 (67.9)	72 (62.6)	133 (58.1)	205 (59.6)	147 (65.6)	282 (62.7)	429 (63.6)
Yes	34 (31.2)	72 (32.6)	106 (32.1)	43 (37.4)	96 (41.9)	139 (40.4)	77 (34.4)	168 (37.3)	245 (36.4)
Age at diagnosis, n (%)									
0-5 years	7 (6.4)	5 (2.3)	12 (3.6)	7 (6.1)	17 (7.4)	24 (7.0)	14 (6.3)	22 (4.9)	36 (5.3)
6-11 years	12 (11.0)	40 (18.1)	52 (15.8)	14 (12.2)	49 (21.4)	63 (18.3)	26 (11.6)	89 (19.8)	115 (17.1)
12-17 years	15 (13.8)	27 (12.2)	42 (12.7)	22 (19.1)	30 (13.1)	52 (15.1)	37 (16.5)	57 (12.7)	94 (13.9)
Disease status, n (%)									
Stable	80 (73.4)	165 (74.7)	245 (74.2)	88 (76.5)	166 (72.5)	254 (73.8)	168 (75.0)	331 (73.6)	499 (74.0)
Progressive	29 (26.6)	56 (25.3)	85 (25.8)	27 (23.5)	63 (27.5)	90 (26.2)	56 (25.0)	119 (26.4)	175 (26.0)
Other autoimmune disorders, n (%)									
No	91 (83.5)	168 (76.0)	259 (78.5)	97 (84.3)	192 (83.8)	289 (84.0)	188 (83.9)	360 (80.0)	548 (81.3)
Yes	18 (16.5)	53 (24.0)	71 (21.5)	18 (15.7)	37 (16.2)	55 (16.0)	36 (16.1)	90 (20.0)	126 (18.7)
F-VASI score[a]									
Mean (SD)	0.999 (0.5942)	0.932 (0.5813)	0.954 (0.5855)	0.834 (0.5233)	0.898 (0.5242)	0.877 (0.5240)	0.915 (0.5638)	0.915 (0.5526)	0.915 (0.5559)
Median	0.740	0.690	0.700	0.600	0.700	0.685	0.695	0.700	0.700
Min, max	0.50, 2.70	0.40, 3.00	0.40, 3.00	0.50, 3.00	0.45, 3.00	0.45, 3.00	0.50, 3.00	0.40, 3.00	0.40, 3.00

Variable	TRuE-V1			TRuE-V2			Pooled Population		
	Vehicle cream (N = 109)	Ruxolitinib cream (N = 221)	Total (N = 330)	Vehicle cream (N = 115)	Ruxolitinib cream (N = 229)	Total (N = 344)	Vehicle cream (N = 224)	Ruxolitinib cream (N = 450)	Total (N = 674)
F-BSA involvement (% of the total body)									
Mean (SD)	1.15 (0.710)	1.05 (0.692)	1.09 (0.698)	0.92 (0.569)	0.98 (0.569)	0.96 (0.569)	1.03 (0.650)	1.02 (0.632)	1.02 (0.638)
Median	0.90	0.80	0.80	0.70	0.80	0.80	0.80	0.80	0.80
Min, max	0.5, 3.0	0.5, 3.0	0.5, 3.0	0.5, 3.0	0.5, 3.0	0.5, 3.0	0.5, 3.0	0.5, 3.0	0.5, 3.0
Categorical summary of F-BSA involvement, n (%)									
< 1.5%	86 (78.9)	172 (77.8)	258 (78.2)	99 (86.1)	189 (82.5)	288 (83.7)	185 (82.6)	361 (80.2)	546 (81.0)
≥ 1.5%	23 (21.1)	49 (22.2)	72 (21.8)	16 (13.9)	40 (17.5)	56 (16.3)	39 (17.4)	89 (19.8)	128 (19.0)
T-VASI score									
Mean (SD)	6.424 (1.9241)	6.489 (2.0228)	6.467 (1.9881)	7.022 (2.1986)	6.830 (2.0645)	6.894 (2.1090)	6.731 (2.0866)	6.662 (2.0490)	6.685 (2.0603)
Median	6.250	6.380	6.340	7.300	7.280	7.295	6.820	6.785	6.795
Min, max	3.06, 10.00	3.01, 10.00	3.01, 10.00	3.10, 10.00	2.65, 10.00	2.65, 10.00	3.06, 10.00	2.65, 10.00	2.65, 10.00
T-BSA involvement (% of the total body)									
Mean (SD)	7.22 (2.008)	7.28 (2.033)	7.26 (2.022)	7.68 (2.040)	7.43 (2.018)	7.51 (2.026)	7.46 (2.033)	7.36 (2.024)	7.39 (2.026)
Median	7.30	7.70	7.60	8.30	7.90	8.00	7.70	7.70	7.70
Min, max	3.7, 10.0	3.2, 10.0	3.2, 10.0	3.6, 10.1	3.5, 10.0	3.5, 10.1	3.6, 10.1	3.2, 10.0	3.2, 10.1
Vitiligo in genital area, n (%)									
No	48 (44.0)	99 (44.8)	147 (44.5)	57 (49.6)	112 (48.9)	169 (49.1)	105 (46.9)	211 (46.9)	316 (46.9)
Yes	61 (56.0)	122 (55.2)	183 (55.5)	58 (50.4)	117 (51.1)	175 (50.9)	119 (53.1)	239 (53.1)	358 (53.1)
Prior therapy given for vitiligo, n (%)									
No	48 (44.0)	90 (40.7)	138 (41.8)	39 (33.9)	86 (37.6)	125 (36.3)	87 (38.8)	176 (39.1)	263 (39.0)
Yes	61 (56.0)	131 (59.3)	192 (58.2)	76 (66.1)	143 (62.4)	219 (63.7)	137 (61.2)	274 (60.9)	411 (61.0)
Topical corticosteroids	28 (25.7)	67 (30.3)	95 (28.8)	28 (24.3)	66 (28.8)	94 (27.3)	56 (25.0)	133 (29.6)	189 (28.0)

Variable	TRuE-V1			TRuE-V2			Pooled Population		
	Vehicle cream (N = 109)	Ruxolitinib cream (N = 221)	Total (N = 330)	Vehicle cream (N = 115)	Ruxolitinib cream (N = 229)	Total (N = 344)	Vehicle cream (N = 224)	Ruxolitinib cream (N = 450)	Total (N = 674)
Vitamin D derivatives	2 (1.8)	4 (1.8)	6 (1.8)	1 (0.9)	0	1 (0.3)	3 (1.3)	4 (0.9)	7 (1.0)
Topical calcineurin inhibitors	31 (28.4)	72 (32.6)	103 (31.2)	37 (32.2)	74 (32.3)	111 (32.3)	68 (30.4)	146 (32.4)	214 (31.8)
Phototherapy	31 (28.4)	61 (27.6)	92 (27.9)	46 (40.0)	77 (33.6)	123 (35.8)	77 (34.4)	138 (30.7)	215 (31.9)
Narrowband ultraviolet B (NB-UVB)	20 (18.3)	41 (18.6)	61 (18.5)	27 (23.5)	52 (22.7)	79 (23.0)	47 (21.0)	93 (20.7)	140 (20.8)
Others									
Psoralen and ultraviolet A (PUVA)	4 (3.7)	8 (3.6)	12 (3.6)	8 (7.0)	15 (6.6)	23 (6.7)	12 (5.4)	23 (5.1)	35 (5.2)
Excimer laser	8 (7.3)	18 (8.1)	26 (7.9)	14 (12.2)	16 (7.0)	30 (8.7)	22 (9.8)	34 (7.6)	56 (8.3)
Other	2 (1.8)	1 (0.5)	3 (0.9)	1 (0.9)	5 (2.2)	6 (1.7)	3 (1.3)	6 (1.3)	9 (1.3)
Surgical techniques	0	0	0	0	1 (0.4)	1 (0.3)	0	1 (0.2)	1 (0.1)
Other therapy									
Oral steroid	2 (1.8)	5 (2.3)	7 (2.1)	0	5 (2.2)	5 (1.5)	2 (0.9)	10 (2.2)	12 (1.8)
Other	7 (6.4)	18 (8.1)	25 (7.6)	13 (11.3)	23 (10.0)	36 (10.5)	20 (8.9)	41 (9.1)	61 (9.1)

Variable	TRuE-V1			TRuE-V2			Pooled Population		
	Vehicle cream (N = 109)	Ruxolitinib cream (N = 221)	Total (N = 330)	Vehicle cream (N = 115)	Ruxolitinib cream (N = 229)	Total (N = 344)	Vehicle cream (N = 224)	Ruxolitinib cream (N = 450)	Total (N = 674)
History of acne vulgaris, n (%)									
No	84 (77.1)	180 (81.4)	264 (80.0)	93 (80.9)	174 (76.0)	267 (77.6)	177 (79.0)	354 (78.7)	531 (78.8)
Yes	25 (22.9)	41 (18.6)	66 (20.0)	22 (19.1)	55 (24.0)	77 (22.4)	47 (21.0)	96 (21.3)	143 (21.2)
Currently have acne vulgaris on the face, n (%)									
No	102 (93.6)	204 (92.3)	306 (92.7)	111 (96.5)	211 (92.1)	322 (93.6)	213 (95.1)	415 (92.2)	628 (93.2)
Yes	7 (6.4)	17 (7.7)	24 (7.3)	4 (3.5)	18 (7.9)	22 (6.4)	11 (4.9)	35 (7.8)	46 (6.8)

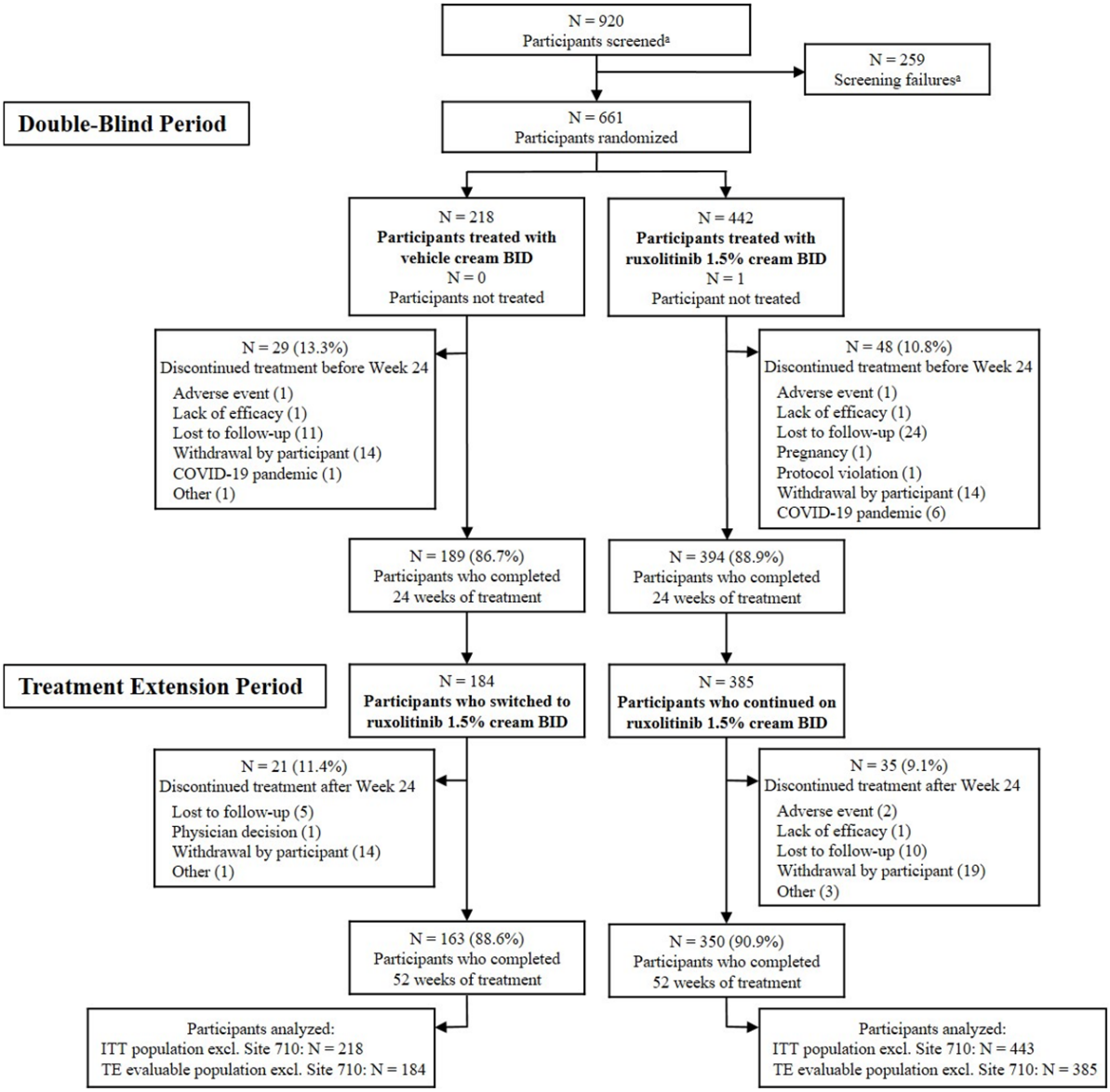
Note: Participants from study site 710 in the TRuE-V2 study are included in the summary of baseline disease characteristics.
Abbreviations: F-BSA, facial body surface area; F-VASI, Face Vitiligo Area Scoring Index; ITT, intention to treat; NB-UVB, narrowband ultraviolet B; PUVA, psoralen and ultraviolet A; SD, standard deviation; TRuE-V1, topical ruxolitinib evaluation in vitiligo study 1; TRuE-V2, topical rlitinib evaluation in vitiligo study 2; T-BSA, total body surface area; T-VASI, total body Vitiligo Area Scoring Index.
[a]Scores on the facial Vitiligo Area Scoring Index (F-VASI) range from 0 to 3, with higher scores indicating a greater area of facial depigmentation.
Source: Summary of clinical efficacy. EMA submission (section 2.7.3) (95); Opzelura assessment report (EMA/135534/2023) (94).

Patient disposition in TRuE-V1 and TRuE-V2

The patient disposition in TRuE-V1 and TRuE-V2 is shown in

Figure *6* (93).

Figure 6. Patient disposition in TRuE-V1 and TRuE-V2 (93)



Source: Opzelura assessment report. (EMA/135534/2023) (94).
Abbreviations: COVID-19, coronavirus disease 2019; ITT, intention to treat; TRuE-V1, topical ruxolitinib evaluation in vitiligo study 1; TRuE-V2, topical ruxolitinib evaluation in vitiligo study 2; TRuE-V LTE, topical ruxolitinib evaluation in vitiligo long-term extension. The ITT population consisted of 661 participants; participants (n = 13) from study site 710 were excluded from the study due to non-compliance with the protocol and concerns with data quality.

B.2.3.2 TRuE-V LTE

TRuE-V LTE is a Phase 3, double-blind, vehicle-controlled, randomised withdrawal and treatment extension study that enrolled eligible patients who have completed either TRuE-V1 or TRuE-V2 (parent studies) in which the patients will have been using ruxolitinib cream for the previous 28 to 52 weeks (depending on their initial randomisation in the parent study; see **Figure 7**) (92). Patients who successfully completed either of the parent studies and tolerated ruxolitinib cream without safety concerns and with good compliance for continuation were eligible to participate in this treatment extension study (92).

Eligible patients in this treatment extension study were assigned to one of two cohorts, Cohort A or Cohort B, based on their F-VASI responses at the time of enrolment in this extension study (i.e., at Week 52) (92).

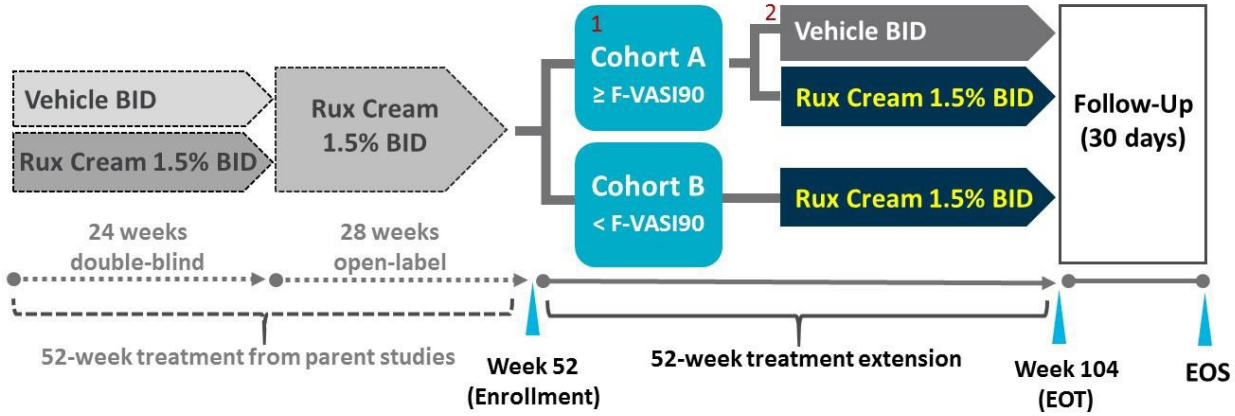
Cohort A

Patients who achieved complete or near-complete facial repigmentation (i.e., achieve F-VASI90) at Week 52 in the parent study were assigned to Cohort A, stratified by the original treatment received on study Day 1 of the parent study, and randomised 1:1 to vehicle cream or ruxolitinib cream for an additional 52 weeks (i.e., until EOT at Week 104). Any patients in Cohort A who experienced relapse (defined as < F-VASI75) received ruxolitinib cream as an open-label rescue treatment until they completed treatment (Week 104 or EOT) (92). In Cohort A, the patient, investigator, and sponsor remained blinded to treatment assignment.

Cohort B

Patients who did not achieve F-VASI90 at Week 52 of the parent studies were assigned to Cohort B and continued ruxolitinib cream for a further 52 weeks (i.e., until EOT at Week 104) (92). Cohort B was open-label (92).

Figure 7. TRuE-V LTE study design schema (92)



Abbreviations: EOS, end of study; EOT, end of treatment; F-VASI90; 90% improvement from baseline in Face Vitiligo Area Scoring Index score; TRuE-V LTE, topical ruxolitinib evaluation in vitiligo long-term extension.
Source: INCB 18424-308 clinical study protocol (amendment 2) (92).
1. All patients in Cohort A will use their randomly assigned treatment (either vehicle or ruxolitinib cream) on both the face and total body.
2. Rescue treatment: If, at any time, a patient in Cohort A loses a clinically meaningful response on the face (< F-VASI75), the patient will receive open-label ruxolitinib cream until Week 104 or EOT.

Demographics and baseline characteristics

Demographic characteristics in Cohort A (patients who had achieved F-VASI90 at Week 52) were generally well-balanced across the treatment groups. Overall, patients were mostly adults (89.7%), while 10.3% of patients were aged 12 to < 18 years. The mean age of patients was 41.1 years (standard deviation [STD]: 14.38 years). The majority of patients were White (77.6%), had Fitzpatrick Skin Type II or III (62.1%), and were female (55.2%) (4).

Patients in Cohort B (patients who had not achieved F-VASI90 at Week 52) were mostly adults (86.5%), while 13.5% of patients were aged 12 to < 18 years. The mean age of patients was 39.4 years (STD: 15.82 years). The majority of patients were White (83.9%), had Fitzpatrick Skin Type II or III (74.0%), and were female (55.6%). There were no meaningful differences between patients initially randomised to ruxolitinib cream and patients initially randomised to vehicle cream in the parent studies (4).

Demographic characteristics of patients in Cohort B were similar to those of patients in Cohort A with 1 exception; a higher proportion of patients in Cohort A had Fitzpatrick Skin Types IV, V, and VI (37.9% vs 24.1%) (**Table 9**) (4).

Table 9. Summary of demographics and baseline characteristics – full analysis set (FAS) population: Cohorts A and B (4)

Cohort A			
Variable	**Vehicle Cream (N = 58)**	**Ruxolitinib Cream (N = 58)**	**Total (N = 116)**
Age (years)			
n	58	58	116
Mean (STD)	39.3 (12.49)	42.9 (15.95)	41.1 (14.38)
Median	40.0	44.0	42.0
Min, max	13, 70	12, 71	12, 71
Age group, n (%)			
12 to < 18 years	4 (6.9)	8 (13.8)	12 (10.3)
18 to < 65 years	53 (91.4)	46 (79.3)	99 (85.3)
≥ 65 years	1 (1.7)	4 (6.9)	5 (4.3)
≤ 40 years	32 (55.2)	21 (36.2)	53 (45.7)
> 40 years	26 (44.8)	37 (63.8)	63 (54.3)
Sex, n (%)			
Male	27 (46.6)	25 (43.1)	52 (44.8)
Female	31 (53.4)	33 (56.9)	64 (55.2)
Skin Type, n (%)			
I	0 (0.0)	0 (0.0)	0 (0.0)
II	15 (25.9)	22 (37.9)	37 (31.9)
III	18 (31.0)	17 (29.3)	35 (30.2)
IV	16 (27.6)	13 (22.4)	29 (25.0)
V	7 (12.1)	4 (6.9)	11 (9.5)
VI	2 (3.4)	2 (3.4)	4 (3.4)
Race, n (%)			
White	42 (72.4)	48 (82.8)	90 (77.6)
Black/African American	5 (8.6)	4 (6.9)	9 (7.8)
Asian	4 (6.9)	3 (5.2)	7 (6.0)
Native Hawaiian or other Pacific Islander	1 (1.7)	0 (0.0)	1 (0.9)
Not reported	2 (3.4)	1 (1.7)	3 (2.6)
Other	4 (6.9)	2 (3.4)	6 (5.2)
Ethnicity, n (%)			
Hispanic or Latino	11 (19.0)	13 (22.4)	24 (20.7)
Not Hispanic or Latino	45 (77.6)	43 (74.1)	88 (75.9)
Not reported	2 (3.4)	1 (1.7)	3 (2.6)

Unknown	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	1 (1.7)	1 (0.9)
Region, n (%)			
North America	40 (69.0)	37 (63.8)	77 (66.4)
Europe	18 (31.0)	21 (36.2)	39 (33.6)
BMI (kg/m^2)			
n	58	58	116
Mean (STD)	25.99 (4.305)	27.06 (5.405)	26.53 (4.895)
Median	25.30	26.83	25.61
Min, max	18.5, 39.7	17.0, 39.9	17.0, 39.9
Cohort B			
Variable	**Vehicle cream to Ruxolitinib cream[a] (N = 118)**	**Ruxolitinib cream to Ruxolitinib cream (N = 224)**	**Total (N = 342)**
Age (years)			
n	118	224	342
Mean (STD)	39.7 (14.62)	39.3 (16.45)	39.4 (15.82)
Median	39.0	39.0	39.0
Min, max	13, 71	12, 79	12, 79
Age group, n (%)			
12 to < 18 years	10 (8.5)	36 (16.1)	46 (13.5)
18 to < 65 years	99 (83.9)	170 (75.9)	269 (78.7)
≥ 65 years	9 (7.6)	18 (8.0)	27 (7.9)
≤ 40 years	71 (60.2)	122 (54.5)	193 (56.4)
> 40 years	47 (39.8)	102 (45.5)	149 (43.6)
Sex, n (%)			
Male	57 (48.3)	95 (42.4)	152 (44.4)
Female	61 (51.7)	129 (57.6)	190 (55.6)
Skin Type, n (%)			
I	1 (0.8)	6 (2.7)	7 (2.0)
II	45 (38.1)	51 (22.8)	96 (28.1)
III	51 (43.2)	106 (47.3)	157 (45.9)
IV	14 (11.9)	43 (19.2)	57 (16.7)
V	6 (5.1)	13 (5.8)	19 (5.6)
VI	1 (0.8)	5 (2.2)	6 (1.8)
Race, n (%)			
White	107 (90.7)	180 (80.4)	287 (83.9)
Black/African American	3 (2.5)	11 (4.9)	14 (4.1)

Asian	3 (2.5)	8 (3.6)	11 (3.2)
American Indian or Alaska Native	0 (0.0)	1 (0.4)	1 (0.3)
Native Hawaiian or other Pacific Islander	0 (0.0)	1 (0.4)	1 (0.3)
Not reported	3 (2.5)	13 (5.8)	16 (4.7)
Other	2 (1.7)	10 (4.5)	12 (3.5)
Ethnicity, n (%)			
Hispanic or Latino	16 (13.6)	53 (23.7)	69 (20.2)
Not Hispanic or Latino	99 (83.9)	157 (70.1)	256 (74.9)
Not reported	3 (2.5)	11 (4.9)	14 (4.1)
Unknown	0 (0.0)	1 (0.4)	1 (0.3)
Other	0 (0.0)	2 (0.9)	2 (0.6)
Region, n (%)			
North America	71 (60.2)	137 (61.2)	208 (60.8)
Europe	47 (39.8)	87 (38.8)	134 (39.2)
BMI (kg/m^2)			
n	118	224	342
Mean (STD)	26.05 (4.892)	26.30 (5.397)	26.21 (5.222)
Median	25.42	26.12	25.72
Min, max	17.4, 39.9	17.0, 46.0	17.0, 46.0

[a]This cohort relates to patients who were switched from vehicle to ruxolitinib cream at Week 24 in the parent studies (TRuE-V1 and TRuE-V2).
Note: Baseline was the last non-missing measurement obtained before or on the day of the first application of study drug in the parent study.
Abbreviations: FAS, full analysis set; STD, standard deviation.
Source: INCB 18424-308 (TRuE-V LTE) clinical study report (4).

Baseline Disease Characteristics

The study population in Cohort A (patients who had achieved ≥ F-VASI90 at Week 52) was largely composed of patients with long-standing vitiligo; the mean time since diagnosis was 13.01 years (STD: 11.002 years) before study entry (see **Table 10**) (4). The majority of patients (70.7%) had stable disease at baseline (4).

Treatment groups were generally well-balanced in terms of disease extent at baseline. The F-VASI score ranged from 0.4 to 3.0 with a median score of 0.7. The F-BSA involvement at baseline ranged from 0.5% to 3.0% with a median of 0.8%. The T-VASI score ranged from 3.1 to 10.0 with a median score of 5.8. The T-BSA involvement at baseline ranged from 3.6% to 10.0% with a median of 6.9% (4).

The study population in Cohort B (patients who had not achieved ≥ F-VASI90 at Week 52) was largely composed of patients with long-standing vitiligo; the mean time since diagnosis was 15.3 years (STD: 11.67 years) before study entry (see **Table 10**) (4). The majority of patients (75.4%) had stable disease at baseline (4).

The F-VASI score ranged from 0.5 to 2.8 with a median score of 0.68. The F-BSA involvement at baseline ranged from 0.5% to 3.0% with a median of 0.8%. The T-VASI score ranged from 2.65 to 10.0 with a median score of 6.85. The T-BSA involvement at baseline ranged from 3.2% to 10.1% with a median of 7.95%. There were no meaningful differences between patients initially randomised to ruxolitinib cream or vehicle cream in the parent studies (4).

Baseline disease characteristics with respect to disease extent and years since diagnosis were similar for patients in Cohorts A and B. Differences in other baseline disease characteristics for Cohorts A and B were as follows (4):

- Patients in Cohort B were more likely to have been diagnosed with vitiligo in childhood (26.7% vs 37.7% for Cohorts A and B, respectively).
- Patients in Cohort B were less likely to have received prior therapy for vitiligo (71.6% vs 60.5% for Cohorts A and B, respectively).
- Patients in Cohort B were less likely to have progressive disease at screening and baseline (29.3% vs 24.6% for Cohorts A and B, respectively).
- Patients in Cohort B were more likely to have a history of acne vulgaris (11.2% vs 24.3% for Cohorts A and B, respectively) and acne vulgaris on the face at screening and baseline (0.9% vs 7.9% for Cohorts A and B, respectively).

Table 10. Summary of baseline disease characteristics (FAS: Cohorts A and B) (4)

Cohort A			
Variable	**Vehicle cream (N = 58)**	**Ruxolitinib cream (N = 58)**	**Total (N = 116)**
Years since initial diagnosis of vitiligo			
n	58	58	116
Mean (STD)	13.10 (9.859)	12.92 (12.125)	13.01 (11.002)
Median	11.61	9.73	10.01
Min, max	0.0, 34.9	0.7, 46.6	0.0, 46.6
Vitiligo diagnosed in childhood, n (%)			
No	42 (72.4)	43 (74.1)	85 (73.3)
Yes	16 (27.6)	15 (25.9)	31 (26.7)
Age at diagnosis, n (%)			
0-5 years	1 (1.7)	4 (6.9)	5 (4.3)
6-11 years	8 (13.8)	10 (17.2)	18 (15.5)
12-17 years	7 (12.1)	1 (1.7)	8 (6.9)
Disease status, n (%)			
Stable	42 (72.4)	40 (69.0)	82 (70.7)
Progressive	16 (27.6)	18 (31.0)	34 (29.3)
Other autoimmune disorders, n (%)			
No	46 (79.3)	48 (82.8)	94 (81.0)
Yes	12 (20.7)	10 (17.2)	22 (19.0)
F-VASI score			
n	58	58	116
Mean (STD)	0.867 (0.4881)	0.987 (0.6382)	0.927 (0.5689)
Median	0.700	0.690	0.700
Min, max	0.50, 3.00	0.40, 3.00	0.40, 3.00
F-BSA involvement (% of the total body)			
n	58	58	116
Mean (STD)	0.92 (0.494)	1.09 (0.739)	1.01 (0.632)
Median	0.80	0.75	0.80
Min, max	0.5, 3.0	0.5, 3.0	0.5, 3.0
Categorical summary of F-BSA involvement, n (%)			
< 1.5%	52 (89.7)	43 (74.1)	95 (81.9)
≥ 1.5%	6 (10.3)	15 (25.9)	21 (18.1)

Cohort A			
Variable	**Vehicle cream (N = 58)**	**Ruxolitinib cream (N = 58)**	**Total (N = 116)**
T-VASI score			
n	58	58	116
Mean (STD)	6.127 (2.1021)	6.295 (2.0233)	6.211 (2.0558)
Median	5.725	5.925	5.800
Min, max	3.10, 10.00	3.10, 10.00	3.10, 10.00
T-BSA involvement (% of the total body)			
n	58	58	116
Mean (STD)	6.84 (2.179)	6.86 (1.912)	6.85 (2.041)
Median	6.70	6.95	6.90
Min, max	3.6, 10.0	3.7, 10.0	3.6, 10.0
Prior therapy given for vitiligo, n (%)			
No	15 (25.9)	18 (31.0)	33 (28.4)
Yes	43 (74.1)	40 (69.0)	83 (71.6)
History of acne vulgaris, n (%)			
No	51 (87.9)	52 (89.7)	103 (88.8)
Yes	7 (12.1)	6 (10.3)	13 (11.2)
Currently have acne vulgaris on the face, n (%)			
No	57 (98.3)	58 (100.0)	115 (99.1)
Yes	1 (1.7)	0 (0.0)	1 (0.9)
Vitiligo in genital area, n (%)			
No	28 (48.3)	31 (53.4)	59 (50.9)
Yes	30 (51.7)	27 (46.6)	57 (49.1)
Cohort B			
Variable	**Vehicle cream to Ruxolitinib cream[a] (N = 118)**	**Ruxolitinib cream to Ruxolitinib cream (N = 224)**	**Total (N = 342)**
Years since initial diagnosis of vitiligo			
n	118	224	342
Mean (STD)	16.16 (11.574)	14.85 (11.717)	15.30 (11.667)
Median	13.63	11.74	12.15
Min, max	0.0, 59.5	0.0, 54.4	0.0, 59.5
Vitiligo diagnosed in childhood, n (%)			
No	75 (63.6)	138 (61.6)	213 (62.3)
Yes	43 (36.4)	86 (38.4)	129 (37.7)

Variable	Vehicle cream to Ruxolitinib cream[a] (N = 118)	Ruxolitinib cream to Ruxolitinib cream (N = 224)	Total (N = 342)
Age at diagnosis, n (%)			
0-5 years	10 (8.5)	9 (4.0)	19 (5.6)
6-11 years	12 (10.2)	48 (21.4)	60 (17.5)
12-17 years	21 (17.8)	29 (12.9)	50 (14.6)
Disease status, n (%)			
Stable	91 (77.1)	167 (74.6)	258 (75.4)
Progressive	27 (22.9)	57 (25.4)	84 (24.6)
Other autoimmune disorders, n (%)			
No	92 (78.0)	182 (81.3)	274 (80.1)
Yes	26 (22.0)	42 (18.8)	68 (19.9)
F-VASI score			
n	118	224	342
Mean (STD)	0.879 (0.5429)	0.911 (0.5526)	0.900 (0.5487)
Median	0.670	0.690	0.680
Min, max	0.50, 2.70	0.50, 2.80	0.50, 2.80
F-BSA involvement (% of the total body)			
n	118	224	342
Mean (STD)	1.01 (0.632)	1.02 (0.637)	1.02 (0.634)
Median	0.80	0.80	0.80
Min, max	0.5, 3.0	0.5, 3.0	0.5, 3.0
Categorical summary of F-BSA involvement, n (%)			
< 1.5%	100 (84.7)	177 (79.0)	277 (81.0)
≥ 1.5%	18 (15.3)	47 (21.0)	65 (19.0)
T-VASI score			
n	118	224	342
Mean (STD)	6.694 (2.1496)	6.730 (2.0203)	6.718 (2.0627)
Median	6.725	6.950	6.850
Min, max	3.06, 10.00	2.65, 10.00	2.65, 10.00
T-BSA involvement (% of the total body)			
n	118	224	342
Mean (STD)	7.42 (2.064)	7.50 (2.000)	7.47 (2.020)
Median	7.60	8.05	7.95
Min, max	3.7, 10.1	3.2, 10.0	3.2, 10.1
Prior therapy given for vitiligo, n (%)			
No	49 (41.5)	86 (38.4)	135 (39.5)

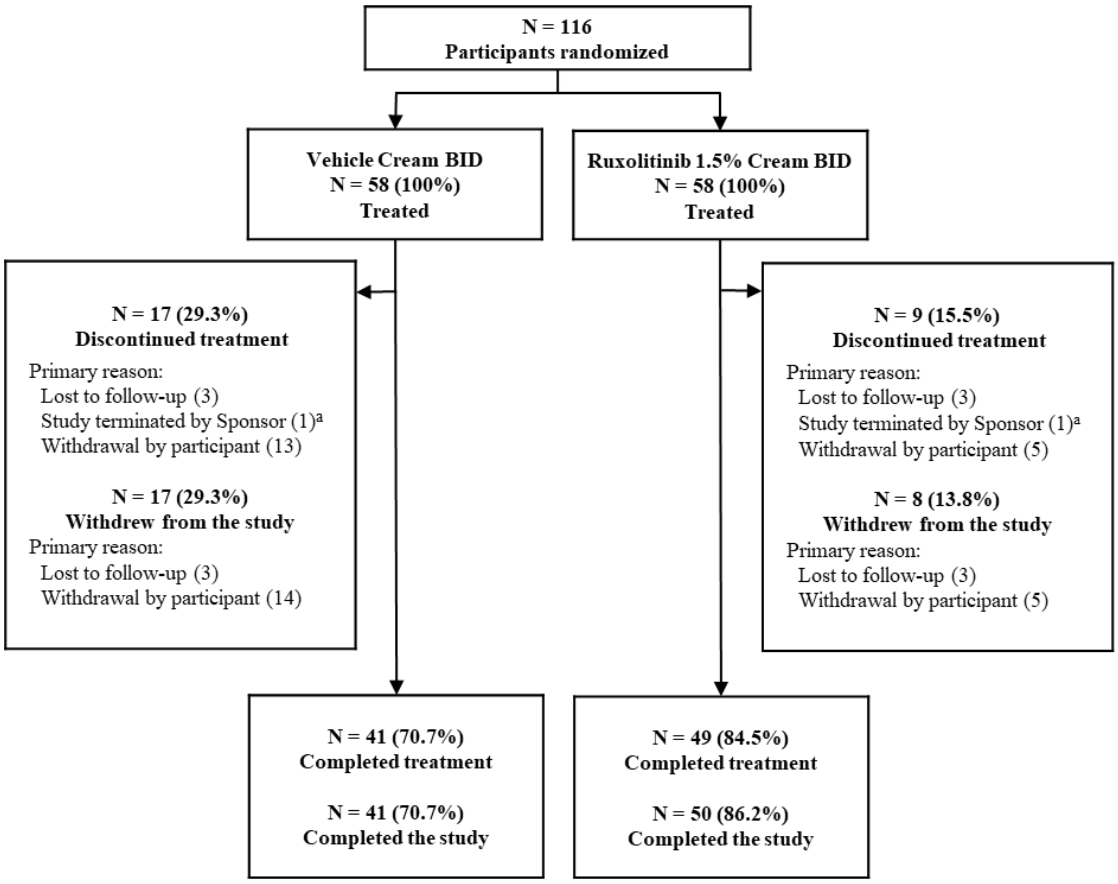
Variable	Vehicle cream to Ruxolitinib cream[a] (N = 118)	Ruxolitinib cream to Ruxolitinib cream (N = 224)	Total (N = 342)
Yes	69 (58.5)	138 (61.6)	207 (60.5)
History of acne vulgaris, n (%)			
No	86 (72.9)	173 (77.2)	259 (75.7)
Yes	32 (27.1)	51 (22.8)	83 (24.3)
Currently have acne vulgaris on the face, n (%)			
No	110 (93.2)	205 (91.5)	315 (92.1)
Yes	8 (6.8)	19 (8.5)	27 (7.9)
Vitiligo in genital area, n (%)			
No	55 (46.6)	110 (49.1)	165 (48.2)
Yes	63 (53.4)	114 (50.9)	177 (51.8)

[a]This cohort relates to patients who were switched from vehicle to ruxolitinib cream at Week 24 in the parent studies (TRuE-V1 and TRuE-V2).
Note: Baseline was the last nonmissing measurement obtained before or on the day of the first application of study drug in the parent study.
Abbreviations: FAS, full analysis set; F-BSA, facial body surface area; F-VASI, facial vitiligo area scoring index; STD, standard deviation; T-BSA, total body surface area.
Source: INCB 18424-308 (TRuE-V LTE) clinical study report (4).

Patient disposition in TRuE-V LTE

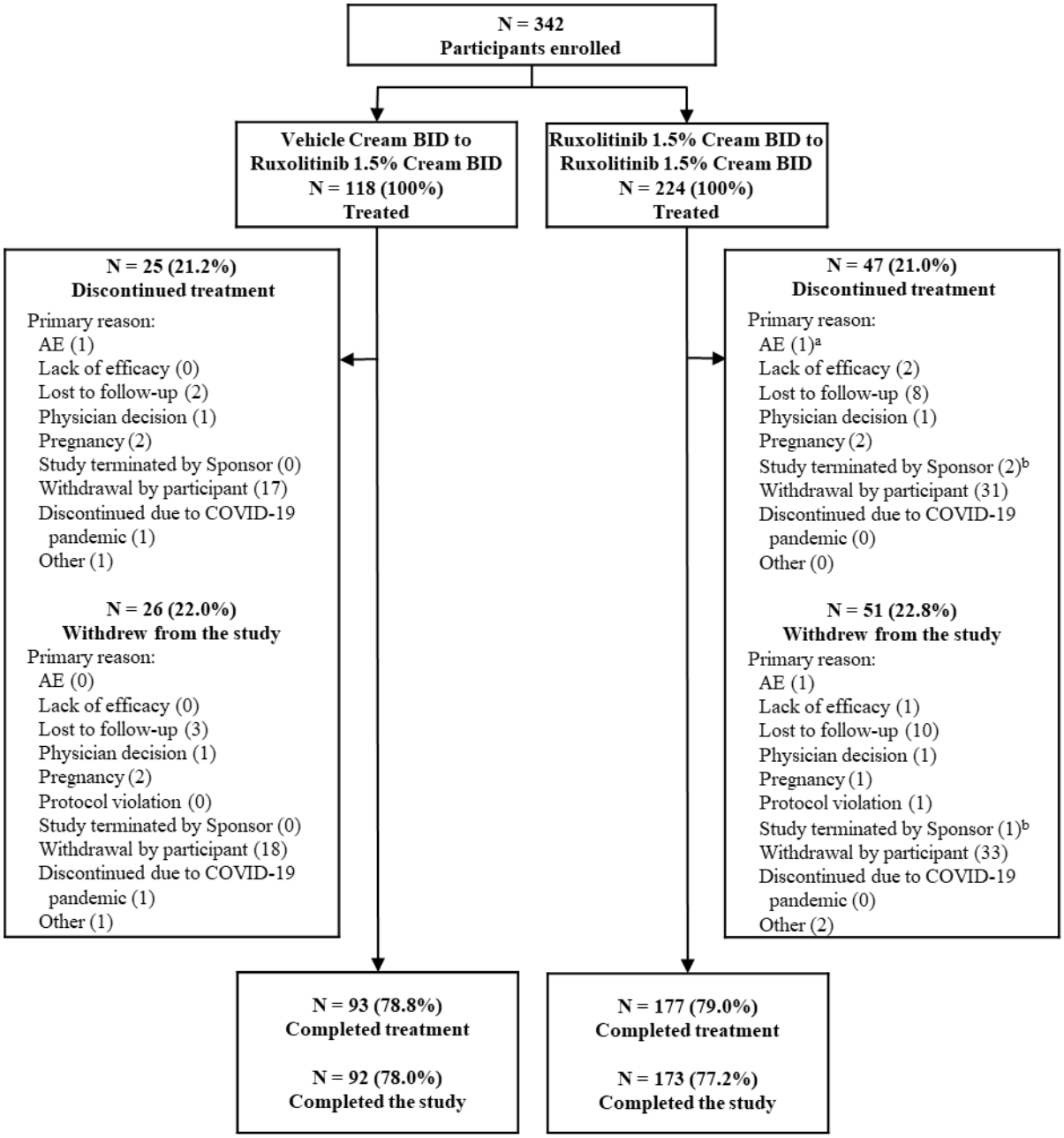
The patient disposition of Cohorts A and B in TRuE-V LTE is shown in **Figure 8** and **Figure 9** (4).

Figure 8. Patient disposition (FAS: Cohort A) (4)



[a] Patient was at Site 710.
Abbreviations: FAS, full analysis set.
Source: INCB 18424-308 (TRuE-V LTE) clinical study report (4).

Figure 9. Patient disposition (FAS: Cohort B) (4)



Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; FAS, full analysis set.
Source: INCB 18424-308 (TRuE-V LTE) clinical study report (4).
Note: The treatment group is based on the actual treatment applied in the parent studies.
[a] The patient had a serious TEAE of acute respiratory failure that led to study drug interruption. The patient was withdrawn from the study due to a TEAE of cardiac ventricular thrombosis with onset while the study drug was interrupted (ie, study drug application was never restarted after the interruption).
[b] Patient(s) was at Site 710.

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

The statistical analysis methods and definitions of study groups used in the pivotal TRuE-V1 and TRuE-V2 trials are described in **Table 11** (2, 3, 90, 91) and **Table 12** (92), respectively.

B.2.4.1 Statistical methods and analysis sets

Table 11. Summary of statistical analysis in the TRuE-V1 and TRuE-V2 trials (2, 3, 90, 91)

Study name (number)	**TRuE-V1 (NCT04052425) and TRuE-V2 (NCT04057573)**
Research hypothesis	The efficacy of ruxolitinib cream is superior to that of vehicle cream
Populations for analysis	• **ITT:** Includes all randomised patients. Treatment groups for this population are defined according to the treatment assignment at randomisation. The ITT population was used for the analyses of efficacy and summaries of demographics, baseline characteristics, and patient disposition. • **Per protocol (PP):** Includes randomised patients who are considered to be sufficiently compliant with the protocol • **Safety:** Includes all patients who applied at least 1 dose of study drug. Treatment groups for this population will be determined according to the actual treatment the patient received on Day 1. • **Pharmacokinetic (PK) / pharmacodynamic (PD) evaluable:** Includes patients who applied at least 1 dose of ruxolitinib cream and provided at least 1 post-dose blood sample for PK. The study pharmacokineticst will review data listings of patient administration and sample records to identify patients to be excluded from the analysis.
Statistical analysis for primary endpoint	For the individual TRuE-V1 and TRuE-V2 studies, the primary alternative hypothesis (superiority of ruxolitinib cream compared with vehicle cream) at Week 24 was tested using exact logistic regression. This model included the treatment group and stratification factors of skin type (Fitzpatrick scale Type I and II or Type III, IV, V, and VI) and geographic region (North America or Europe). The unadjusted p value between the ruxolitinib cream group versus vehicle was compared at 2 sided $\alpha = 0.05$ level. Odds ratio (OR) and 95% CIs in response rates (ruxolitinib cream vs vehicle) at Week 24 were also computed. The primary endpoint was also examined for the PP population using the same model as the primary analysis.
Statistical analysis for key secondary and exploratory endpoints	Key secondary efficacy endpoints for binary outcomes (F-VASI 50, F-VASI90 and T-VASI 50) were analysed using similar methods to those specified in the primary analysis. For the continuous outcome (the percent change from baseline in F-BSA at Week 24) an analysis of covariance (ANCOVA) model was used with treatment group, stratification factors, and baseline value as covariates. A test for superiority between ruxolitinib cream and vehicle cream was performed using the least squares mean (LSM) estimate of the percent change from baseline in F-BSA at Week 24 from the ANCOVA model. Superiority was established if the p value of the difference (ruxolitinib cream minus vehicle) was less than 0.05. For continuous secondary efficacy endpoints, a mixed-effect model with repeated measurements was fit for the comparisons between ruxolitinib cream cream group and vehicle cream group. For categorical secondary endpoints, a similar exact logistic regression models as specified in the primary and key secondary analysis was used if applicable.
Sample size & power calculation	Approximately 300 patients were randomised 2:1 to ruxolitinib cream or vehicle and stratified by baseline skin type (Fitzpatrick scale Type I and II vs Type III, IV, V, and VI) and region (North America or Europe); adolescents made up at least 10% of the study population. The sample size is calculated to provide sufficient power (> 85%) to detect a difference between the ruxolitinib cream with the vehicle in primary and key secondary endpoints.
Data management, patient withdrawals	The coronavirus disease 2019 (COVID-19) pandemic had an impact on the clinical study participation, which led to both increased discontinuations and missed efficacy assessments. To minimise potential bias from missing values and the impact on study interpretation, multiple imputation was used to replace non-responder imputation (NRI) as the primary method for handling missing values in the analyses of the primary and key secondary endpoints. All patients who were missing the F-VASI assessment at a given visit in the double-blind period were handled using multiple imputation under the missing-at-random assumption. For multiple imputation, a fully conditional specification method that assumes the existence of a joint distribution for all variables was used to impute the numerical score. Sensitivity analyses performed on the primary endpoint include: • Non-responder imputation. Participants who were missing postbaseline values were defined as non-responders.

	• Last observed non-missing post-baseline value was used to fill in missing values at Week 24. • A tipping point sensitivity analysis was conducted to examine the potential effects of missing data. The missing F-VASI75 response at Week 24 in each treatment group was replaced by a range of values from the most conservative case (all missing is non-response) to the most aggressive case (all missing is response).
Abbreviations: ANCOVA; analysis of covariance; COVID-19, coronavirus disease 2019; F-BSA, facial body surface area; F-VASI 50, 50% improvement from baseline in face vitiligo area scoring index score; F-VASI 75, 75% improvement from baseline in face vitiligo area scoring index score; F-VASI 90, 90% improvement from baseline in face vitiligo area scoring index score; ITT, intention to treat; LSM, least squares mean; NRI, non-responder imputation; OR, odds ratio; PK, phamacokinetic; PP, per protocol; TRuE-V1, topical ruxolitinib evaluation in vitiligo study 1; TRuE-V2, topical ruxolitinib evaluation in vitiligo study 2; T-VASI 50, 50% improvement in total body Vitiligo Area Scoring Index. Source: INCB 18424-306 CSR; INCB 18424-307 CSR; Opzelura assessment report (EMA/135534/2023) (2, 3, 94)	

Table 12. Summary of statistical analysis in TRuE-V LTE (92)

Study name (number)	TRuE-V LTE (NCT04530344)
Populations for analysis	• **FAS:** All participants enrolled in the study who receive at least 1 dose of study drug (ruxolitinib cream or vehicle) at or after Week 52.[a] • **ITT in long-term extension (ITT-Ext):** All participants who achieve ≥ F-VASI90 at Week 52[a] and are randomised. Treatment groups for this population were defined according to the treatment assignment at the time of randomisation regardless of the actual study medication the participant might have taken in the study. • **PK evaluable:** The PK evaluable population includes participants who received at least 1 dose of ruxolitinib cream and provided at least 1 measurable post-dose PK sample/assessment. The study pharmacokineticist reviewed data listings of participant administration and sample records to identify participants to be excluded from the analysis. • **PK/PD evaluable:** The PK/PD evaluable population included participants who received at least 1 dose of study drug (ruxolitinib cream or vehicle) and provided at least 1 measurable/evaluable post-dose PK/PD sample/assessment. The study pharmacokineticist reviewed data listings of participant administration and sample records to identify participants to be excluded from the analysis.
Efficacy analysis	• For all complete or near-complete responders in the ITT-Ext population (defined as achieving F-VASI90 at Week 52) in the treatment extension period, the events can be defined as follows: - Relapse is defined as a loss of F-VASI75 response assessed as percentage change from the baseline (Day 1 of the parent study) on F-VASI < 75%. - Loss of complete or near-complete response is defined as participants who do not maintain an F-VASI90. • For relapse, a binary variable event is defined to be equal to 1 (Yes) when the value is greater or equal to 75% and 0 (No) for less than 50%. • For loss of F-VASI90 response, a categorical variable event is defined to be equal to 1 (Yes) when the value is greater or equal to 90% and 0 (No) for less than 90%. • The time to relapse or loss of adequate response is defined as the number of days from the Week 52 randomisation to the first evaluation date at which the participant has met the criteria. • For participants who discontinue early or who complete without meeting criteria for the event, the time-to-event was censored and defined as the number of days from the Week 52 randomisation to the participant's last evaluation date. • The time to event data was assessed using the Kaplan-Meier product limit method. Treatment comparisons between ruxolitinib cream to vehicle were performed using the log-rank test. Hazard ratios and the corresponding 95% confidence intervals were estimated using the Cox proportional hazards model. • The incidence of relapse or loss of adequate response following the Week 52 randomisation were summarised by ruxolitinib cream and vehicle at each timepoint. • For all relapse participants, the time to regaining F-VASI75/90 response is defined as the number of days from the start of the retreatment of ruxolitinib cream to the first visit at which the participant has regained the F-VASI75/90 response. For participants who discontinued or completed treatment before regaining F-VASI75/90, the time to regaining F-VASI75/90 is censored. The time to event data was assessed using the Kaplan-Meier product limit method.
Sample size & power calculation	Any eligible participants were enrolled from the 2 parent Phase 3 studies, TRuE-V1 and TRuE-V2. The sample size is not based on any statistical power calculations.

Data management, patient withdrawals

For the primary and secondary endpoints, the algorithm below was applied to determine censoring or event:

Situation	Date of relapse / lost response, or censoring	Outcome
Relapse / lost response documented on or between scheduled visits	Date of relapse / lost response	Relapsed / lost response
No relapse / maintain response	Date of last assessment	Censored
Treatment discontinuation	Date of last assessment	Censored
Applying rescue treatment (ruxolitinib cream) in extension treatment period without relapse / lost response status	Date of rescue treatment	Censored

For all other endpoints, no imputation was performed for missing values, unless otherwise specified.

Abbreviations: F-VASI 75, 75% improvement from baseline in face vitiligo area scoring index score; F-VASI 90, 90% improvement from baseline in face vitiligo area scoring index score; ITT-Ext, intention to treat long-term extension; PD, pharmacodynamic; PK, pharmacokinetic; TRuE-V1, topical ruxolitinib evaluation in vitiligo study 1; TRuE-V2, topical ruxolitinib evaluation in vitiligo study 2; TRuE-V LTE, topical ruxolitinib evaluation in vitiligo study long-term extension.

[a] Week 52 is the first visit of the treatment extension study (visits are named to reflect continuation from the parent study).

Source: INCB 18424-308 (TRuE-V LTE) clinical study report; INCB 18424-308 clinical study protocol (amendment 2) (4, 92).

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

Quality assessment for each trial included in the SLR is presented in Appendix D. A summary of the quality assessment of TRuE-V1, TRuE-V2 and TRuE-V LTE is shown in **Table 13** (4, 93).

Table 13. Quality assessment of the TRuE-V studies (4, 93)

	TRuE-V1 and TRuE-V2 (93)	TRuE-V LTE (4)
Was the method used to generate random allocations adequate?	Yes, all participants were centrally assigned to study treatment using an interactive response technology system	In Cohort A, yes - all participants were centrally assigned to study treatment using an interactive response technology system. In Cohort B, no - the treatment was open-label.
Was the allocation adequately concealed?	Yes, allocation generated by automated system	In Cohort A, yes - the participant, investigator, and sponsor remained blinded to treatment assignment until after database lock for the primary analysis (Week 104). In Cohort B, no - the treatment was open-label.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes, the distribution of baseline characteristics was similar across trial groups for both trials.	Yes, the distribution of baseline characteristics was similar across trial groups for both trials.
Were the care providers, participants, and outcome assessors blind to treatment allocation?	Yes, double-blind design	In Cohort A, yes - the participant, investigator, and sponsor remained blinded to treatment assignment until after database lock for the primary analysis (Week 104). In Cohort B, no - the treatment for Cohort B was open-label.
Were there any unexpected imbalances in dropouts between groups?	No, drop-out rates were similar between the groups	In Cohort A, yes – the drop-out rate was higher in the vehicle cream group (29.3%) vs in the ruxolitinib cream group (15.5%). In Cohort B, no – drop-out rates were similar between groups (21%).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No, all outcomes cited in the protocol are reported in the clinical study report (CSR)	No, all outcomes cited in the protocol are reported in CSR
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes, the ITT population constituted the primary analysis set. Multiple imputation was used as the primary method for handling missing values in the	Yes, outcomes reported for FAS using appropriate methods to account for missing data described in ***Table 12***.

	analyses of the primary and key secondary endpoints.	

Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination).
Abbreviations: CRD, centre for reviews and dissemination; CSR, clinical study report; FAS, full analysis set; ITT, intention to treat; TRuE-V1, topical ruxolitinib evaluation in vitiligo study 1; TRuE-V2, topical ruxolitinib evaluation in vitiligo study 2; TRuE-V LTE, topical ruxolitinib evaluation in vitiligo study long-term extension.

B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1 Pivotal trials (TRuE-V1 and TRuE-V2)

The primary evaluation of the efficacy of ruxolitinib cream in this submission is based on pooled data from TRuE-V1 and TRuE-V2 (2, 3). Data from the ITT population constituted the primary analysis set. The set consisted of 109 and 221 participants in the vehicle and ruxolitinib groups, respectively for TRuE-V1, and 109 and 222 participants, respectively for TRuE-V2 (excluding participants [n = 13] from study site 710 due to non-compliance with the protocol) (94).

For TRuE-V1, 90 participants in the vehicle group entered the treatment extension phase, of whom 82 (91%) completed 52 weeks of treatment; 193 participants in the ruxolitinib cream group entered the treatment extension phase and 174 (90%) completed treatment. For TRuE-V2, 102 participants in the vehicle group entered the treatment extension phase, of whom 81 (83%) completed 52 weeks of treatment, whereas 206 participants in the ruxolitinib cream group entered the treatment extension phase, of whom 182 (92%) completed treatment (94).

The results for pooled analyses for the primary and key secondary endpoints from the Phase 3 studies are presented. In addition, subgroup analyses were conducted for the primary endpoint in the pooled population. The database for the pooled efficacy analyses includes data from the double blind, vehicle-controlled period of the confirmatory Phase 3 studies (2, 3, 90, 91, 93, 94).

B.2.6.1.1 Primary endpoint: Proportion of patients achieving F-VASI75 at Week 24

In the pooled analysis of both Phase 3 confirmatory studies (TRuE-V1 and TRuE-V2), the proportion of patients achieving F-VASI75 at Week 24 was statistically significantly higher in the ruxolitinib cream group (30.7%) compared with the vehicle cream treatment group (9.6%) (OR = 4.17, $p < 0.0001$; see **Table 14** and **Figure 10**) (90, 91, 94). In both TRuE-

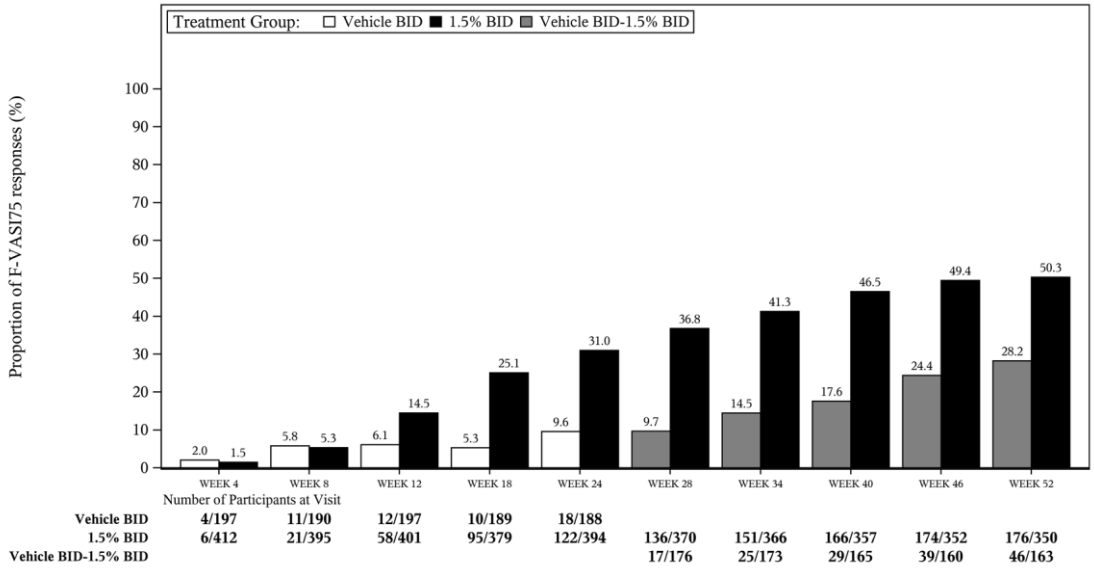
V1 and TRuE-V2, the proportion of patients achieving F-VASI75 at Week 24 was statistically significantly higher in the ruxolitinib cream group compared with the vehicle cream treatment group (OR = 5.28, p < 0.0001 for TRuE-V1, and OR = 3.45, p = 0.0021 for TRuE-V2, respectively; see **Table 14**) (90, 91, 94).

Table 14. Summary and analysis of patients achieving F-VASI75 at Week 24 (ITT Population) (90, 91, 94)

Endpoint	TRuE-V1		TRuE-V2		Pooled Analysis	
	Vehicle cream (N = 109)	Ruxolitinib cream (N = 221)	Vehicle cream (N = 109)	Ruxolitinib cream (N = 222)	Vehicle cream (N = 218)	Ruxolitinib cream (N = 443)
Multiple imputation[a]						
Estimated F-VASI75 response rate (%) (SE)	7.4 (2.65)	29.8 (3.21)	11.4 (3.20)	30.9 (3.27)	9.6 (2.17)	30.7 (2.29)
Response rate difference (SE)[b]	—	22.3 (4.15)	—	19.5 (4.56)	—	21.1 (3.18)
95% CI	—	(14.214, 30.471)	—	(10.537, 28.420)	—	(14.853, 27.342)
Active treatment vs vehicle						
Odds ratio (95% CI)[c]	—	5.28 (2.341, 11.903)	—	3.45 (1.737, 6.835)	—	4.17 (2.434, 7.142)
p-value	—	< 0.0001	—	0.0004	—	< 0.0001
NRI[d]						
F-VASI75 response rate (%) (SE)	6.4 (2.35)	27.1 (2.99)	10.1 (2.89)	27.9 (3.01)	8.3 (1.86)	27.5 (2.12)
Response rate difference (SE)[e]	—	20.7 (3.80)	—	17.8 (4.17)	—	19.3 (2.82)
Active treatment vs vehicle						
Odds ratio (95% CI)**Error! Reference source not found.**	—	5.43 (2.353, 14.655)	—	3.42 (1.683,7.546)	—	4.21 (2.461, 7.570)
p-value	—	< 0.0001	—	0.0002	—	< 0.0001
LOCF[f]						
Estimated F-VASI75 response rate (%) (SE)	7.0 (2.55)	28.5 (3.09)	11.4 (3.10)	29.4 (3.14)	9.3 (2.03)	28.9 (2.20)
Response rate difference (SE)[e]	—	21.5 (4.00)	—	18.0 (4.41)	—	19.7 (2.99)
Active treatment vs vehicle						
Odds ratio (95% CI)**Error! Reference source not found.**	—	5.25 (2.272, 14.189)	—	3.18 (1.593, 6.833)	—	3.96 (2.334, 7.032)
p-value	—	< 0.0001	—	0.0004	—	< 0.0001

Note: Data from study site 710 were excluded.
Abbreviations: CI, confidence interval; F-VASI75, 75% improvement from baseline in Face Vitiligo Area Scoring Index score; ITT, intention to treat; LOCF, last observation carried forward; NRI, non-responder imputation; SE, standard error.
Source: EMA Opzelura assessment report (EMA/135534/2023) (94).

Figure 10. Proportion of patients achieving F-VASI75 during the double-blind period (ITT Pooled Population) (94)



Note: Data from study site 710 were excluded.
Abbreviations: F-VASI75, 75% improvement from baseline in face vitiligo area scoring index score; ITT, intention to treat.
Source: Opzelura assessment report (EMA/135534/2023) (94).

B.2.6.1.2 Secondary endpoints

Results of analyses of key secondary endpoints in the confirmatory Phase 3 studies (TRuE-V1 and TRuE-V2) are summarised in **Table 15** (94). In the pooled analyses, the clinical effects obtained with the ruxolitinib cream treatment regimen at Week 24 were statistically significantly improved compared with those in the vehicle cream treatment group for all key secondary endpoints. The proportions of patients achieving F-VASI50, F-VASI90, T-VASI50, and a VNS score of 4 or 5 (vitiligo "a lot less noticeable" or "no longer noticeable"), as well as the percent change from baseline in F-BSA were statistically significantly higher for the ruxolitinib cream group compared with the vehicle cream treatment group (90, 91, 94).

Table 15. Summary of results for key secondary endpoints (ITT Population) (90, 91, 94)

Endpoint	TRuE-V1		TRuE-V2		Pooled Analysis	
	Vehicle cream (N = 109)	**Ruxolitinib cream (N = 221)**	**Vehicle cream (N = 109)**	**Ruxolitinib cream (N = 222)**	**Vehicle cream (N = 218)**	**Ruxolitinib cream (N = 443)**
Estimated F-VASI50 response rate (%) (SE) at Week 24	16.9 (3.89)	51.2 (3.46)	20.9 (4.06)	51.4 (3.50)	19.6 (2.89)	51.7 (2.46)
Response rate difference (SE)[a]	—	34.2 (5.18)	—	30.6 (5.36)	—	32.2 (3.83)
95% CI	—	(24.092, 44.408)	—	(20.048, 41.061)	—	(24.646, 39.672)
Active treatment vs vehicle						
Odds ratio (95% CI)[b]	—	5.18 (2.831, 9.482)	—	3.99 (2.296, 6.949)	—	4.40 (2.918, 6.647)
p-value	—	< 0.0001	—	< 0.0001	—	< 0.0001
Estimated F-VASI90 response rate (%) (SE) at Week 24	2.2 (1.51)	15.3 (2.50)	1.3 (1.25)	16.3 (2.62)	1.9 (1.01)	16.0 (1.83)
Response rate difference (SE)[a]	—	13.2 (2.89)	—	15.0 (2.92)	—	14.2 (2.09)
95% CI	—	(7.497, 18.839)	—	(9.250, 20.702)	—	(10.080, 18.274)
Active treatment vs vehicle						
Odds ratio (95% CI)[b]	—	8.49 (1.997, 36.048)	—	15.29 (2.150, 108.739)	—	10.33 (3.310, 32.210)
p-value	—	0.0038	—	0.0065	—	< 0.0001
Estimated T-VASI50 response rate (%) (SE) at Week 24	5.1 (2.34)	20.6 (2.76)	6.8 (2.50)	23.9 (2.97)	5.8 (1.64)	21.9 (2.04)
Response rate difference (SE)[a]	—	15.5 (3.63)	—	17.1 (3.87)	—	16.1 (2.62)
95% CI	—	(8.339, 22.592)	—	(9.538, 24.721)	—	(10.910, 21.200)
Active treatment vs vehicle						
Odds ratio (95% CI)[b]	—	4.93 (1.795, 13.566)	—	4.29 (1.865, 9.853)	—	4.55 (2.419, 8.577)
p-value	—	0.0020	—	0.0006	—	< 0.0001
Estimated VNS scores of 4 or 5 response rate (%) (SE) at Week 24	3.3 (1.85)	24.5 (3.03)	4.9 (2.17)	20.5 (2.85)	4.2 (1.45)	22.5 (2.09)
Response rate difference (SE)[a]	—	21.2 (3.54)	—	15.5 (3.58)	—	18.3 (2.53)
95% CI	—	(14.271, 28.143)	—	(8.515, 22.561)	—	(13.317, 23.246)
Active treatment vs vehicle						
Odds ratio (95% CI)[b]	—	9.53 (2.900, 31.290)	—	4.86 (1.851, 12.755)	—	6.52 (3.114, 13.667)

Endpoint	TRuE-V1		TRuE-V2		Pooled Analysis	
	Vehicle cream (N = 109)	Ruxolitinib cream (N = 221)	Vehicle cream (N = 109)	Ruxolitinib cream (N = 222)	Vehicle cream (N = 218)	Ruxolitinib cream (N = 443)
p-value	—	0.0002	—	0.0013	—	< 0.0001
Percent change from baseline in F-BSA score at Week 24						
ANCOVA[c]						
LSM (SE)	−9.5 (3.25)	−28.9 (2.22)	−7.0 (3.82)	−26.4 (2.57)	−7.9 (2.63)	−27.8 (1.75)
95% CI	(−15.90, −3.17)	(−33.23, −24.53)	(−14.45, 0.53)	(−31.45, −21.39)	(−13.02, −2.69)	(−31.29, −24.41)
Active treatment vs vehicle						
LSM difference (SE)	—	−19.3 (3.93)	—	−19.5 (4.59)	—	−20.0 (3.17)
95% CI	—	(−27.05, −11.64)	—	(−28.46, −10.45)	—	(−26.22, −13.77)
Between-group p-value	—	< 0.0001	—	< 0.0001	—	< 0.0001

Note: Multiple imputation: missing VASI scores and F-BSA were imputed by fully conditional specification. The multiple imputation method uses treatment and observed stratification factors as predicators.
Note: P-values from exact logistic regression: [response at Week 24 = treatment + stratification factors (Fitzpatrick skin type I and II vs Fitzpatrick skin type III, IV, V, and VI, Region North America/Europe)].
Note: Data from study site 710 were excluded.
[a] $p < 0.0001$, ruxolitinib cream vs vehicle.
[b] $p < 0.01$ ruxolitinib cream vs vehicle.
[c] $p = 0.0159$ ruxolitinib cream vs vehicle.
Abbreviations: ANOVA, analysis of covariance; CI, confidence interval; F-BSA, facial body surface area; F-VASI50, ≥ 50% improvement from baseline in Face Vitiligo Area Scoring Index score; F-VASI90, ≥ 90% improvement from baseline in Face Vitiligo Area Scoring Index score; LSM, least squares mean; SE, standard error; T-VASI50, ≥ 50% improvement in total body Vitiligo Area Scoring Index; VNS, vitiligo noticeability scale.
Source: EMA. Opzelura assessment report (EMA/135534/2023) (94).

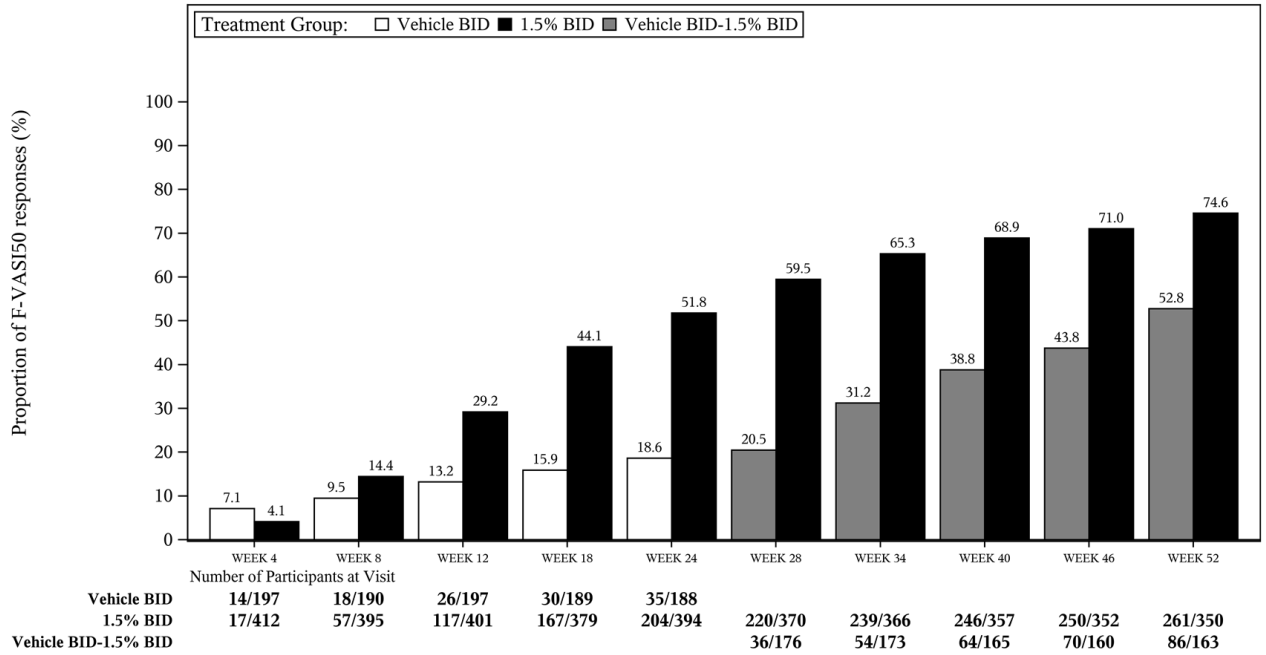
Proportion of patients achieving F-VASI50 and F-VASI90 at Week 24

Trends similar to F-VASI75 were seen in the proportion of patients achieving F-VASI50 and F-VASI90 in both confirmatory studies (TRuE-V1 and TRuE-V2). In the pooled analysis, the proportions of patients achieving F-VASI50 and F-VASI90 increased through Week 24, with clear separation for the active treatment group from the vehicle treatment group by Week 12 (see **Figure 11**) (90, 91, 94).

In the pooled results, 51.7% of the participants in the ruxolitinib cream group and 19.6% in the vehicle group achieved at least 50% repigmentation after 24 weeks of treatment (F-VASI50), with a response rate difference of 32.2% ($p < 0.0001$), and almost complete repigmentation (F-VASI90) was reached in 16% in the ruxolitinib cream group versus 1.9% in the vehicle group after 24 weeks of treatment, with a response rate difference of 14.2% ($p < 0.0001$) (see **Table 15** and **Figure 11**) (94).

Figure 11. Proportion of patients achieving F-VASI50 and F-VASI90 during the double-blind period (ITT pooled population) (90, 91, 94)

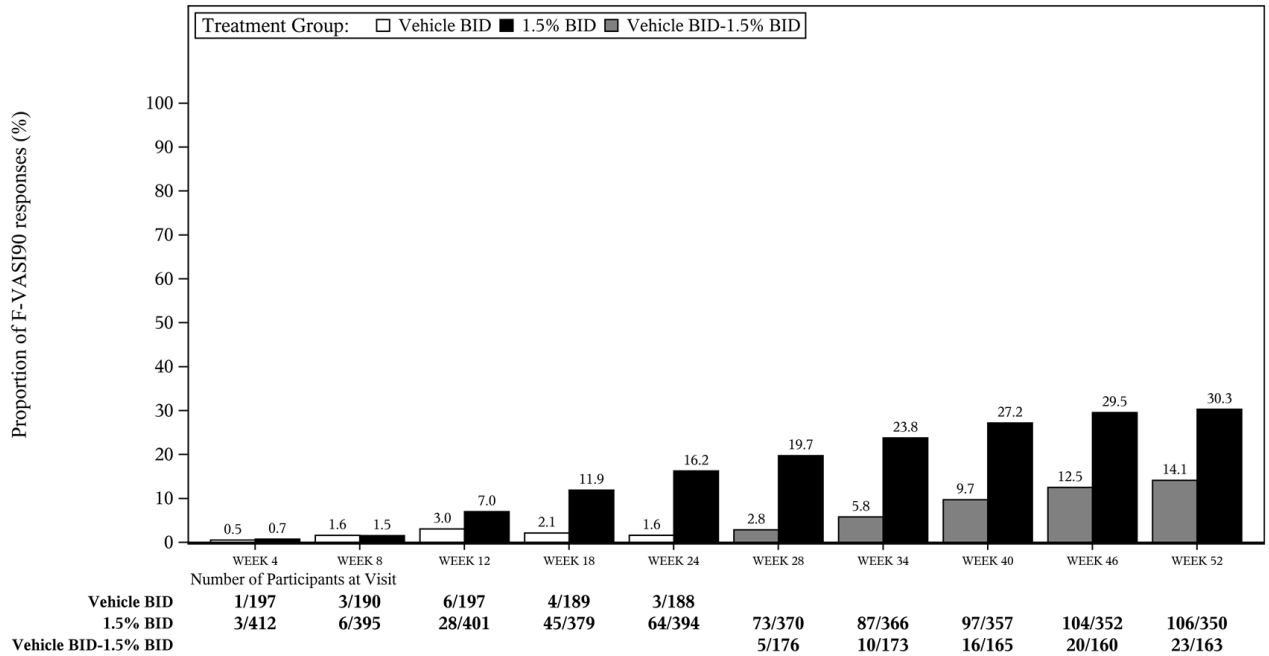
F-VASI50



Number of Participants at Visit

	WEEK 4	WEEK 8	WEEK 12	WEEK 18	WEEK 24	WEEK 28	WEEK 34	WEEK 40	WEEK 46	WEEK 52
Vehicle BID	14/197	18/190	26/197	30/189	35/188					
1.5% BID	17/412	57/395	117/401	167/379	204/394	220/370	239/366	246/357	250/352	261/350
Vehicle BID-1.5% BID						36/176	54/173	64/165	70/160	86/163

F-VASI90



Number of Participants at Visit

	WEEK 4	WEEK 8	WEEK 12	WEEK 18	WEEK 24	WEEK 28	WEEK 34	WEEK 40	WEEK 46	WEEK 52
Vehicle BID	1/197	3/190	6/197	4/189	3/188					
1.5% BID	3/412	6/395	28/401	45/379	64/394	73/370	87/366	97/357	104/352	106/350
Vehicle BID-1.5% BID						5/176	10/173	16/165	20/160	23/163

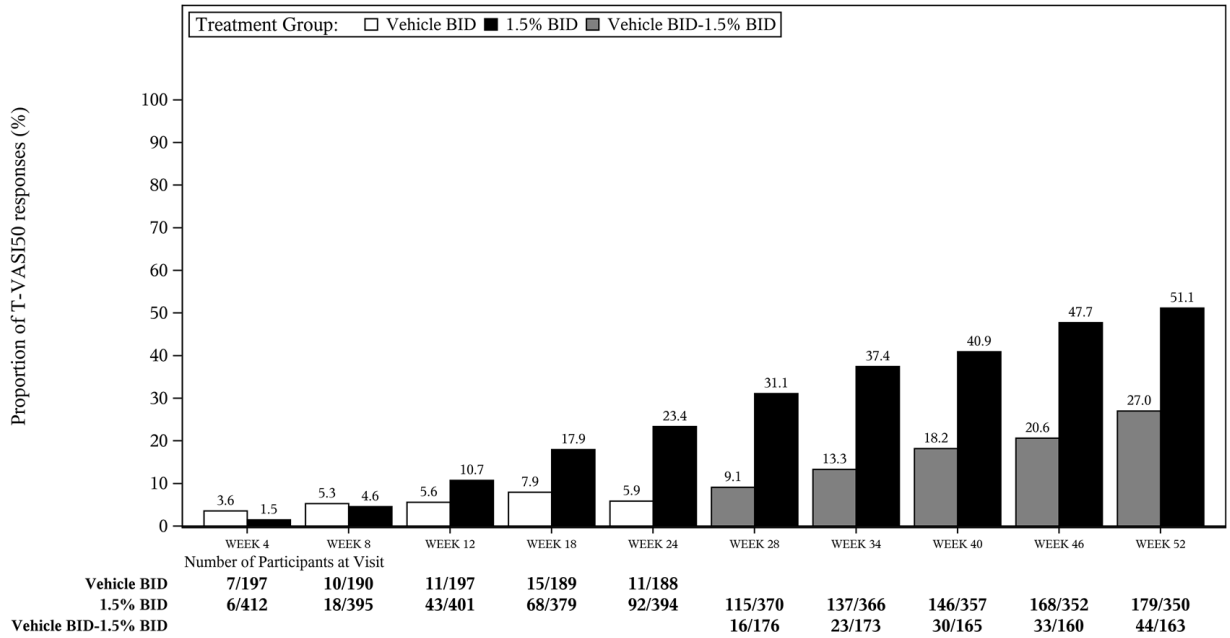
Note: Data from study site 710 were excluded.
Abbreviations: F-VASI50, ≥ 50% improvement from baseline in face vitiligo area scoring index score; F-VASI90, ≥ 90% improvement from baseline in Face Vitiligo Area Scoring Index score; ITT, intention to treat.

Source: EMA. Opzelura assessment report (EMA/135534/2023) (94).

Proportion of patients achieving T-VASI50 at Week 24

On average, patients were almost four times more likely (21.9% vs 5.8%) to achieve at least 50% repigmentation across the whole body with ruxolitinib cream compared to vehicle cream (see **Table 15** and **Figure 12**) (94).

Figure 12. Proportion of patients achieving T-VASI50 at Week 24 (ITT pooled population) (94)



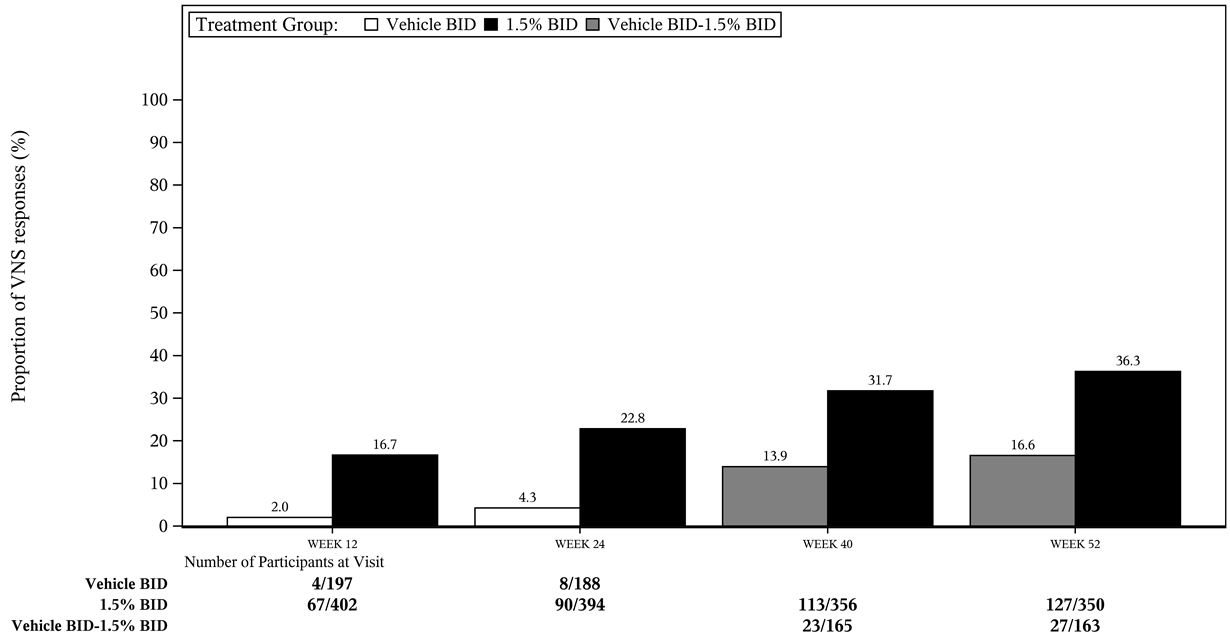
Note: Data from study site 710 were excluded.
Abbreviations: ITT, intention to treat; T-VASI50, ≥ 50% improvement in total body vitiligo area scoring index.
Source: EMA. Opzelura assessment report (EMA/135534/2023) (94).

Proportion of patients achieving a VNS score of 4 or 5 at Week 24

The proportion of patients reporting a VNS score of 4 or 5 (vitiligo "a lot less noticeable" or "no longer noticeable") increased from Week 12 to Week 24 in the ruxolitinib cream group while the proportion remained low in the vehicle group. The proportion of patients reporting a VNS score of 4 or 5 was larger in the ruxolitinib cream group (22.5%) compared to the vehicle group (4.2%), with a treatment effect of 18.3% ($p < 0.0001$) (see **Table 15** and **Figure 13**) (90, 91, 94). The pattern of improvement to achieve a VNS score of 4 or 5 continued during the treatment-extension period for patients who continued on ruxolitinib cream, although the number of patients at later timepoints is smaller as the treatment-extension period is ongoing. A similar pattern of improvement from Week 24

onwards was observed for patients who crossed over from vehicle cream in the double-blind period to ruxolitinib cream in the treatment-extension period (94). At Week 52, 127/350 patients (36.3%) achieved a VNS response of 4 or 5 (94).

Figure 13: Proportion of patients achieving a VNS score of 4 or 5 (ITT Pooled Population) (90, 91, 94)



Note: Data from study site 710 were excluded.
Abbreviations: ITT, intention to treat; VNS, vitiligo noticeability scale.
Source: EMA. Opzelura assessment report (EMA/135534/2023) (94).

F-VASI50, F-VASI75, T-VASI50, VNS 4 or 5 and F-BSA up to Week 52

Proportions of patients reaching the F-VASI75, F-VASI50, F-VASI90, T-VASI50, VNS score 4 or 5, and changes in F-BSA, F-VASI, and T-VASI during both the double-blind 24 weeks period as well as during the treatment extension phase up to 52 weeks are presented in section 2.6.5 in the European Medicines Agency (EMA) Opzelura assessment report (EMA/135534/2023) (94); see appendix C.

B.2.6.1.3 Exploratory endpoints

F-PhGVA, T-PhGVA, F-PaGIC-V, T-PaGIC-V, DLQI, CDLQI, VitiQoL and colour matching up to Week 52

While DLQI is a widely used patient-reported outcome (PRO) instrument that was collected in the TRuE-V studies, it is not sufficiently specific and sensitive to capture nuances on how patients with vitiligo handle their overall disease burden (64). Conversely, part of the DLQI questionnaire is related to symptoms that are less relevant to vitiligo (96). As an alternative to DLQI, VitiQoL was also captured in the TRuE-V studies. It is a disease specific HRQoL tool that emphasises three primary factors, namely behaviour, participation limitation and stigma, however, this tool has not been validated for the assessment of responsiveness over time (96).

Both TRuE-V1 and TRuE-V2 reported statistically significant improvements with ruxolitinib cream vs vehicle cream at Week 24 in the colour matching question score of 1–3, F-PaGIC-V score of 1 or 2, F-PhGVA score of 0 or 1, and T-PaGIC-V score of 1 or 2. TRuE-V2 reported a statistically significant improvement with ruxolitinib cream vs vehicle cream at Week 24 in T-PhGVA, whereas TRuE-V1 reported a numerically but not statistically significant improvement in T-PhGVA (94). Both TRuE-V1 and TRuE-V2 reported no statistically significant between-group differences in changes in DLQI, CDLQI and VitiQoL (94). Detailed results of these exploratory outcomes up to Week 52 are presented in section 2.6.5 in the EMA Opzelura assessment report (EMA/135534/2023) (94); see appendix C.

HADS at Week 24

A numerically greater improvement in the mean change from baseline in HADS total score of depression was observed with ruxolitinib cream compared to vehicle cream at Week 24 (LSM difference: −0.2; p = 0.3728 [95% CI: -0.63,0.24]) (**Table 16**) (97). Similarly, a numerically higher improvement in the mean change from baseline in HADS total score of anxiety was observed with ruxolitinib cream compared to vehicle cream (LSM difference: −0.1; p = 0.6124 [95% CI: -0.63,0.37]) (**Table 17**) (97).

Table 16. Summary of HADS total score of depression during the double blind treatment period (ITT population) (97)

	Vehicle cream (N=224)	Ruxolitinib cream (N=450)
Change from baseline in HADS Total Score of Depression at Week 24		
N	190	400
Mean	-0.02	-0.16
STD	2.836	2.926
Min	-11.0	-14.0
Median	0.00	0.00
Max	8.0	9.0
ANCOVA[1]		
LSM (SE)	0.0 (0.18)	-0.2 (0.12)
95% CI	(-0.33, 0.38)	(-0.42, 0.07)
Treatment – vehicle		
LSM difference		-0.2 (0.22)
95% CI		(-0.63, 0.24)
Between-group p-value		0.3728

Note: [1] MMRM model: [Response Variable = Treatment + Stratification Factors (Skin Type Fitzpatrick scale Type I and II vs Type III, IV, V, and VI, Region
North America/Europe) + Visit + Treatment*Vi
Note: All the patients took ruxolitinib cream after Week 24.
Abbreviations: CI, confidence interval; HADS, Hospital Anxiety and Depression Scale; ITT, intention to treat; LSM, least square mean; SE, standard error; STD, standard deviation.
Source: Incyte. INCB018424-306/307 HADS analysis. Table 99.9.1 [Data on file] (97).

Table 17. Summary of HADS total score of anxiety during the double blind treatment period (ITT population) (97)

	Vehicle cream (N=224)	Ruxolitinib cream (N=450)
Change from baseline in HADS Total Score of Anxiety at Week 24		
N	190	400
Mean	-0.43	-0.50
STD	3.126	3.329
Min	-10.0	-13.0
Median	0.00	0.00
Max	11.0	12.0
ANCOVA[1]		
LSM (SE)	-0.4 (0.21)	-0.5 (0.14)
95% CI	(-0.80, 0.03)	(-0.8, -0.23)
Treatment – vehicle		
LSM difference		-0.1 (0.25)
95% CI		(-0.63, 0.37)
Between-group p-value		0.6124

Note: [1] MMRM model: [Response Variable = Treatment + Stratification Factors (Skin Type Fitzpatrick scale Type I and II vs Type III, IV, V, and VI, Region North America/Europe) + Visit + Treatment*Vi Note: All the patients took ruxolitinib cream after Week 24.
Abbreviations: CI, confidence interval; HADS, Hospital Anxiety and Depression Scale; LSM, least square mean; SE, standard error; STD, standard deviation.
Source: Incyte. INCB018424-306/307 HADS analysis. Table 99.9.2 [Data on file] (97).

B.2.6.2 Withdrawal and treatment extension study (TRuE-V LTE)

B.2.6.2.1 Primary endpoint: Time to relapse (< F-VASI75)

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 did not experience relapse (< F-VASI75) while on study; 69.1% and 39.3% of patients in the ruxolitinib cream and vehicle cream treatment groups, respectively, did not experience relapse through Week 104 (4).

The median time to relapse (< F-VASI75) was not evaluable (NE) for either the ruxolitinib cream group (95% CI: NE, NE) or the vehicle cream treatment group (95% CI: 238.0, NE) due to the small number of patients who experienced relapse (see **Table 18** and **Figure 14**) (4). Half of the relapse events occurred within approximately 4 months (112 days) after treatment discontinuation. Fewer patients experienced relapse in the ruxolitinib cream group (14.5%) compared with the vehicle cream group (28.6%), and the risk of relapse was significantly lower for patients who continued to apply ruxolitinib cream beyond Week 52 compared with patients who applied vehicle cream after Week 52 (hazard ratio [HR]: 0.422 [95% CI: 0.180, 0.990], p = 0.0414) (4).

Table 18. Summary and analysis of time to relapse (ITT-Ext population) (4)

Variable	Vehicle cream (N = 56)	Ruxolitinib cream (N = 55)
Number (%) of patients with event	16 (28.6)	8 (14.5)
Number (%) of patients censored	40 (71.4)	47 (85.5)
End of treatment	22 (39.3)	38 (69.1)
Treatment discontinuation	13 (23.2)	7 (12.7)
Rescue treatment without relapse	5 (8.9)	2 (3.6)
Median time to relapse (days)		
95% CI	NE (238.0, NE)	NE (NE, NE)
Treatment/vehicle[a]		
HR	—	0.422
95% CI	—	(0.180, 0.990)
p-value	—	0.0414

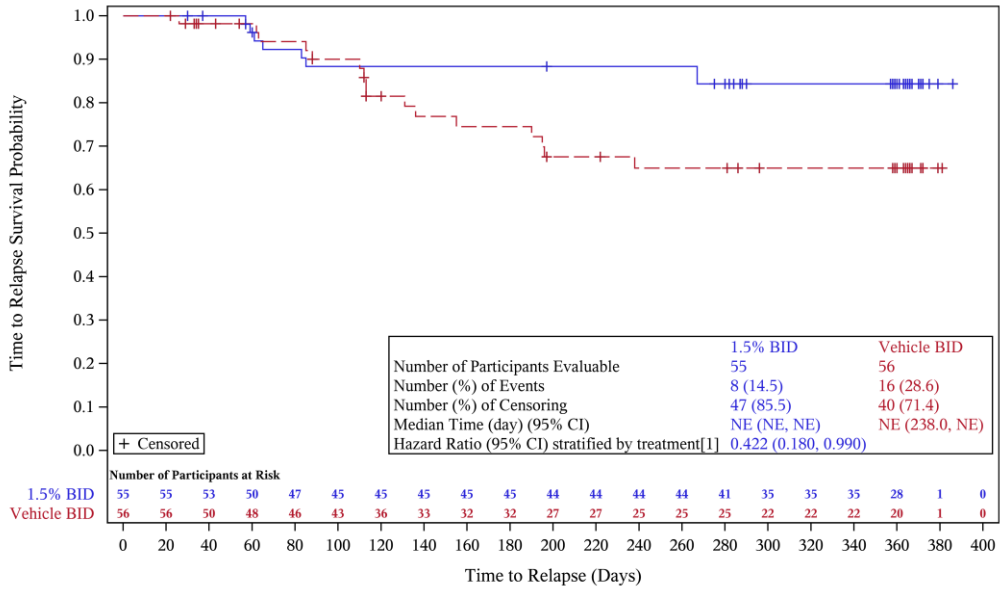
Note: Relapse was defined as a loss of F-VASI75 response, assessed as percentage improvement in the F-VASI score at baseline (Day 1 of the parent study) to < 75%.

[a] Cox regression model stratified by stratification factor (treatment assignment in the parent studies) was conducted to compare the difference in hazard rate between treatment and vehicle. The p-value was based on the log-rank test stratified by randomisation stratification factor between treatment and vehicle.

Abbreviations: CI, confidence interval; HR, hazard ratio; ITT-Ext, intention to treat in long-term extension; NE, not evaluable.

Source: INCB 18424-308 (TRuE-V LTE) Clinical Study Report (4).

Figure 14. Kaplan-Meier curve of the time to relapse (ITT-Ext population) (4)



Note: Relapse is defined as a loss of F-VASI75 response, assessed as percentage improvement in the F-VASI score at baseline (Day 1 of the parent study) to < 75%.

Abbreviations: CI, confidence interval; ITT-Ext, intention to treat in long-term extension; NE, not evaluable.

Source: INCB 18424-308 (TRuE-V LTE) Clinical Study Report (4).

B2.6.2.2 Key secondary endpoints

Time to maintain F-VASI90 response

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, while 21.4% of patients who applied vehicle cream and then switched to ruxolitinib cream at Week 24 maintained at least 90% of facial repigmentation through Week 104 (see **Table 19** and **Figure 15**) (4).

Of the cohort of patients who received vehicle cream then switched to ruxolitinib cream at Week 24 and subsequently achieved an F-VASI90 response, 55.4% lost their F-VASI90 response (see **Table 19Error! Reference source not found.**) (4). The median time to loss of F-VASI90 was 195.0 days (95% CI: 113.0, 372.0). Of the Cohort of patients who applied ruxolitinib cream in the double-blind period then continued treatment with ruxolitinib and achieved an F-VASI90 response, 23.6% lost their F-VASI90 response (4). The median tme to loss of F-VASI90 response in this cohort was not evaluable (4).

The risk of losing F-VASI90 response was significantly lower for patients who continued to use ruxolitinib cream compared with patients who applied vehicle cream (HR: 0.316 [95% CI: 0.165, 0.606], p = 0.0003) (4).

Table 19. Summary and analysis of the time to maintain F-VASI90 response (ITT-Ext population) (4)

Variable	Vehicle cream (N = 56)	Ruxolitinib cream (N = 55)
Number (%) of patients with event	31 (55.4)	13 (23.6)
Number (%) of patients censored	25 (44.6)	42 (76.4)
End of treatment	12 (21.4)	34 (61.8)
Treatment discontinuation	10 (17.9)	6 (10.9)
Rescue treatment without lost response	3 (5.4)	2 (3.6)
Median time to loss of adequate response (days)		
95% CI	195.0 (113.0, 372.0)	NE (NE, NE)
Treatment/vehicle[a]		
HR	—	0.316
95% CI	—	(0.165, 0.606)
p-value	—	0.0003

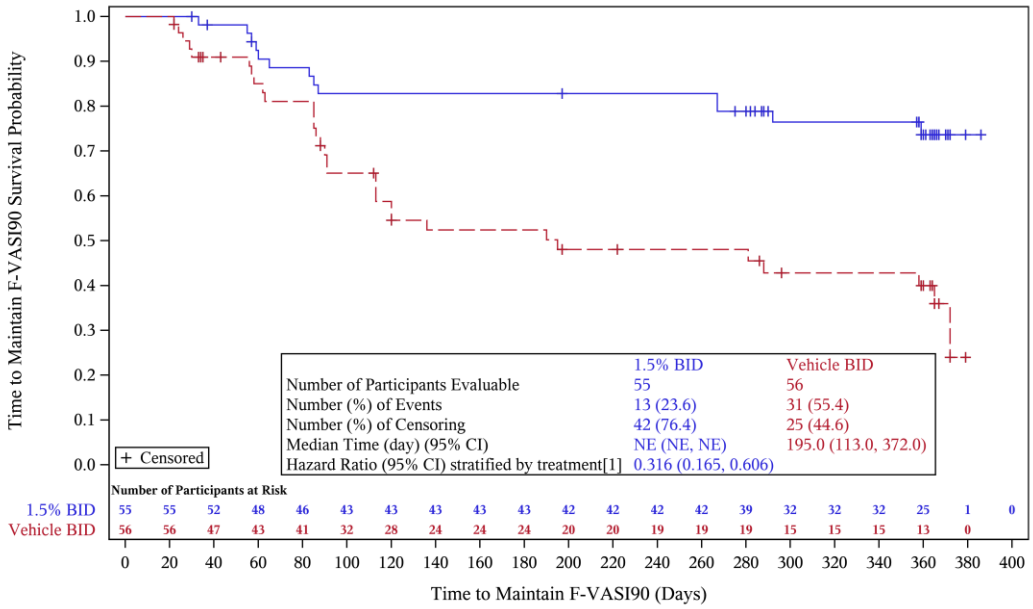
Note: Loss of adequate response is defined as a loss of F-VASI90 response, assessed as percentage improvement in the F-VASI score at baseline (Day 1 of the parent study) to < 90%.

[a] Cox regression model stratified by stratification factor (treatment assignment in the parent studies) was conducted to compare the difference in hazard rate between treatment and vehicle. The p-value was based on the log-rank test stratified by randomisation stratification factor between treatment and vehicle.

Abbreviations: CI, confidence interval; ITT-Ext, intention to treat in long-term extension; NE, not evaluable.

Source: INCB 18424-308 (TRuE-V LTE) Clinical Study Report (4).

Figure 15. Kaplan-Meier curve for the time to maintain F-VASI90 response (ITT-Ext population) (4)



Note: Loss of adequate response is defined as a loss of F-VASI90 response, assessed as percentage improvement in the F-VASI score at baseline (Day 1 of the parent study) to < 90%.

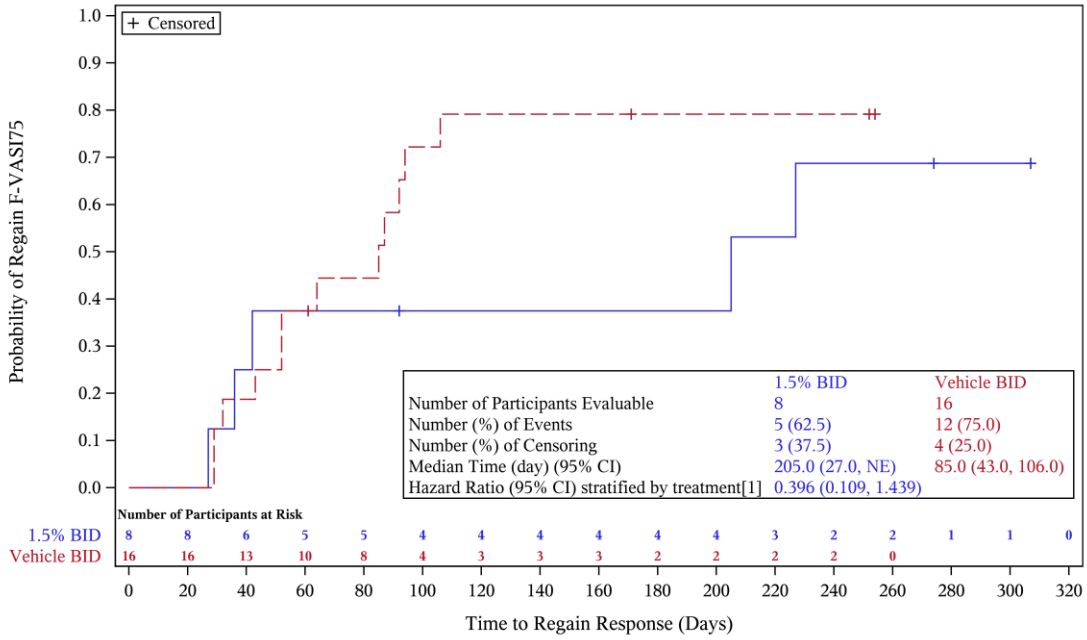
Note: The HR stratification factor was the initial treatment assigned in the parent studies.

Abbreviations: CI, confidence interval; F-VASI90, 90% improvement from baseline in Face Vitiligo Area Scoring Index Score; ITT-Ext, intention to treat in long-term extension; NE, not evaluable.
Source: INCB 18424-308 (TRuE-V LTE) Clinical Study Report (4).

Time to regain F-VASI response

The median time to regain F-VASI75 for patients randomised to vehicle cream in Cohort A (patients who had achieved F-VASI90 at Week 52) who experienced relapse (< F-VASI75) and received open-label rescue treatment was 85.0 days (95% CI: 43.0, 106.0; see **Figure 16**) (4). Although some patients randomised to ruxolitinib cream in Cohort A experienced relapse, the majority (5 of 8 patients [62.5%]) regained F-VASI75 with continued application of ruxolitinib cream; the median time to regain F-VASI75 was 205.0 days (95% CI: 0.109, 1.439) (4).

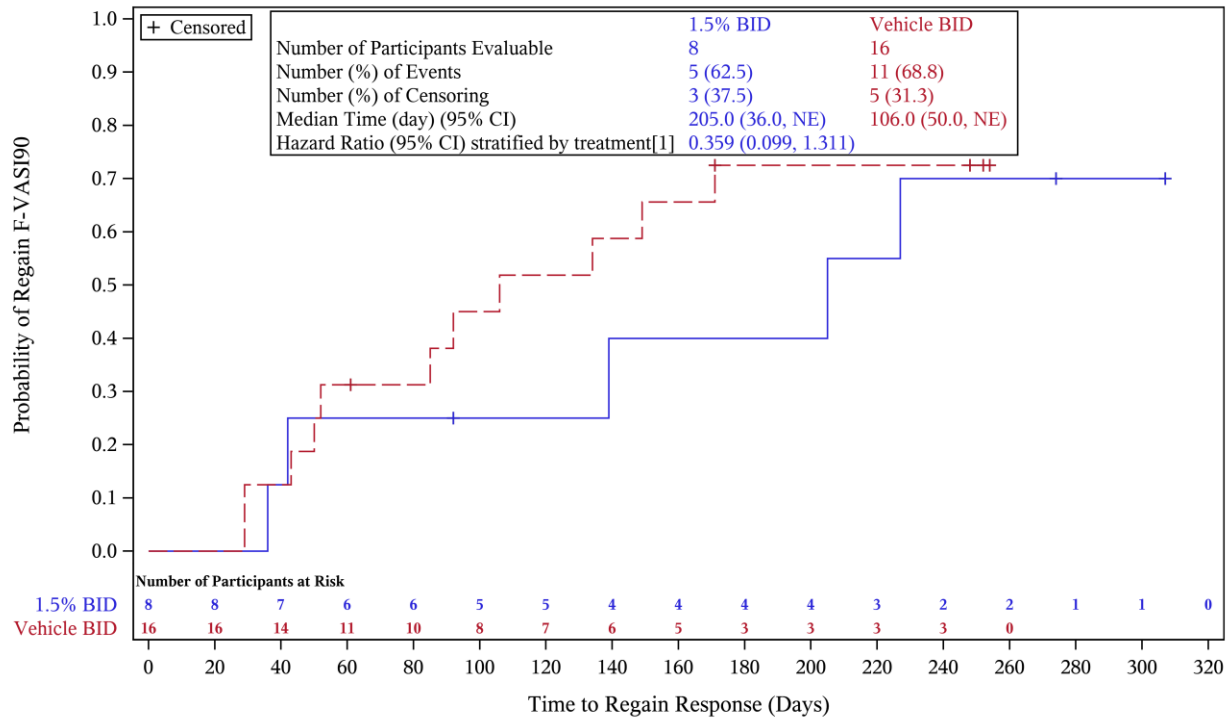
Figure 16. Kaplan-Meier curve of the time to regain F-VASI75 response (4)



Abbreviations: CI, confidence interval; F-VASI75, 75% improvement from baseline in Face Vitiligo Area Scoring Index Score; NE, not evaluable.
Source: INCB 18424-308 (TRuE-V LTE) Clinical Study Report (4).
Note: The HR stratification factor was the initial treatment assigned in the parent studies.

The median time to regain F-VASI90 for patients randomised to vehicle cream in Cohort A who experienced relapse and received open-label rescue treatment was 106.0 days (95% CI: 50.0, NE; see **Figure 17**) (4). The median time to regain F-VASI90 for patients randomised to ruxolitinib cream in Cohort A who experienced relapse and continued to apply ruxolitinib cream was 205.0 days (95% CI: 36.0, NE) (4).

Figure 17. Kaplan-Meier curve of the time to regain F-VASI90 response (4)



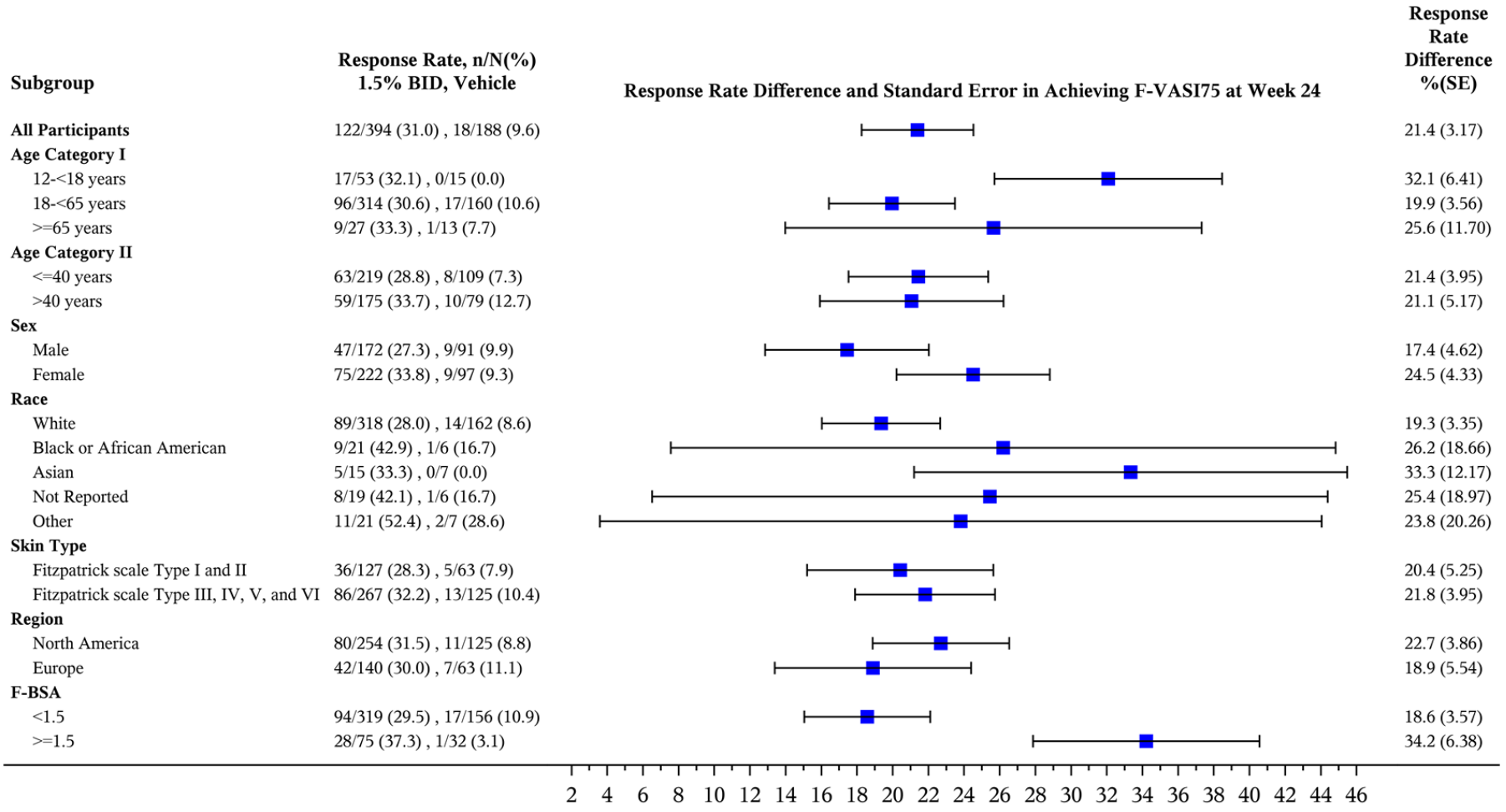
Abbreviations: CI, confidence interval; F-VASI90, 90% improvement from baseline in Face Vitiligo Area Scoring Index Score; NE, not evaluable.
Source: INCB 18424-308 (TRuE-V LTE) Clinical Study Report (4).
Note: The HR stratification factor was the initial treatment assigned in the parent studies.

B.2.7 Subgroup analysis

Subgroup analyses of the proportion of patients in the pooled Phase 3 population achieving F-VASI75 at Week 24 were performed to assess the consistency of the ruxolitinib cream treatment effect based on intrinsic (age group, sex, race, skin type, and baseline F-BSA score) and extrinsic (geographic region) factors (90, 91, 94).

A forest plot for the differences between the ruxolitinib cream and vehicle cream treatment groups in response rate in achieving F-VASI75 is provided in **Figure 18** (90, 91). Patients in the ruxolitinib cream group consistently had a better response than those in the vehicle cream treatment group regardless of subgroup, although variability was observed in the magnitude of response within each subgroup (90, 91, 94).

Figure 18. Forest plot of response rate difference between ruxolitinib cream vs vehicle in the proportion of patients achieving F-VASI75 at Week 24 (ITT pooled population) (90, 91, 94)



Note: Data from participants enrolled at Site 710 in the TRuE-V2 study were excluded.
Abbreviations: F-BSA, facial body surface area; F-VASI75, ≥ 75% improvement from baseline in Face Vitiligo Area Scoring Index score; ITT, intention to treat; SE, standard error.
Source: EMA. Opzelura assessment report (EMA/135534/2023) (94).

Additional subgroup analyses of F-VASI75 for the double-blind period were performed for the subgroups of baseline disease status (stable and progressive disease) and prior vitiligo therapy (TCS, TCI and phototherapy). The results were consistent with those from the total population through Week 24: patients in the ruxolitinib cream group consistently had a better response than those in the vehicle cream group regardless of subgroup (see **Table 20Error! Reference source not found.**) (90, 91).

Table 20. Summary of patients achieving F-VASI75 at Week 24 by disease status and prior therapy (ITT Pooled Population) (2, 3)

Subgroup	Vehicle cream	Ruxolitinib cream
All patients, n/N (%)	18/188 (9.6)	122/394 (31)
Response rate difference* (SE)	—	21.4 (3.17)
Baseline disease status		
Stable disease, n/N (%)	11/141 (7.8)	87/287 (30.3)
Response rate difference (SE)	—	21.6 (3.53)
Progressive disease, n/N (%)	7/47 (14.9)	35/107 (32.7)
Response rate difference (SE)	—	17.8 (6.89)
Prior vitiligo therapy		
Topical corticosteroids, n/N (%)	4/44 (9.1)	39/120 (32.2)
Response rate difference (SE)	—	23.4 (6.09)
Topical calcineurin inhibitors, n/N (%)	4/62 (6.5)	44/136 (32.4)
Response rate difference (SE)	—	25.9 (5.08)
Phototherapy, n/N (%)	5/64 (7.8)	43/126 (34.1)
Response rate difference (SE)	—	26.3 (5.39)

Note: Data from participants enrolled at Site 710 in the TRuE-V2 study were excluded.
Abbreviations: F-VASI75, ≥ 75% improvement from baseline in face vitiligo area scoring index score; ITT, intention to treat; SE, standard error. *Ruxolitinib cream vs Vehicle
Source: EMA. Opzelura assessment report (EMA/135534/2023) (94).

Due to the anticipated positioning of ruxolitinib cream, the subgroup “prior therapy” is used in the base case of the cost-effectiveness analysis, and additional analyses are presented using the ITT population and the subgroup “Fitzpatrick Skin Type IV-VI”. Data used in the

economic model for the overall population and the subgroup “Fitzpatrick skin type IV-VI” are provided in Appendix M.

B.2.8 Meta-analysis

Pooled data from the identically designed Phase 3 trials (TRuE-V1 and TRuE-V2) is presented in the preceding sections.

B.2.9 Indirect and mixed treatment comparisons

As stated in the decision problem, ruxolitinib cream is anticipated to be positioned as a step change option between first and second line for adults and adolescents from 12 years of age with NSV with facial involvement. Notwithstanding this positioning in the treatment pathway, an assessment was conducted to also investigate the feasibility of deriving treatment effect estimates for ruxolitinib cream relative to TCS, TCI and phototherapy.

B.2.9.1 Indirect treatment comparison objective

Results from the aforementioned SLR were used to assess the feasibility of a robust ITC to estimate the relative efficacy of ruxolitinib cream versus other therapies.

B2.9.2 ITC methods

The SLR was conducted in March 2022 and subsequently updated in January 2023 to identify evidence from studies assessing the clinical efficacy of therapies in vitiligo. The review included adults and adolescents with vitiligo (any type). Prior to the ITC, a comprehensive FA was conducted to verify the transitivity assumption, i.e., the similarity of study designs and patient populations across included studies, and the possibility of synthesising the available evidence for specific efficacy outcomes, patient reported outcomes (PROs) and safety outcomes. Summarising the findings of the aforementioned SLR and its revised version, 253 studies were identified for clinical outcomes, 180 studies reported safety outcomes, and 23 studies reported QoL outcomes. A large proportion of included studies reported more than one type of outcome. **Table 21** provides the screening process for the ITC FA.

Table 21. Screening process for the papers identified in the SLR (including the SLR update) against the ITC feasibility criteria

	Efficacy	QoL	Safety
Number of studies screened from the SLR	253	23	180
Treatment characteristic criteria not satisfied	*-121*	*-7*	*-86*
Number of studies	132	16	94
Outcomes of interest not reported	*-122*	*-8*	*-71*
Number of studies included in feasibility assessment	10	8	23

Abbreviations: ITC, Indirect treatment comparison; PICOS, Population, Intervention, Comparator, Outcomes, Study design; QoL, quality of life; SLR, Systematic literature review.
Two trials (Rothstein et al. and Wu et al.) were excluded from the counts in this table[1]
Source: Appendix D.

Twenty-four (unique) potential comparator studies were identified and included in the FA with four studies related to ruxolitinib cream (TRuE-V1, TRuE-V2, TRuE-V LTE, in addition to the Phase 2 study [NCT03099304]), amounting to a total of 28 studies eligible for the ITC FA. Interventions assessed in these studies included broadband ultraviolet B (BB-UVB), NB-UVB, UVA, PUVA, tacrolimus, pimecrolimus, mometasone furoate, clobetasol, hydrocortisone acetate, minocycline, superoxide dismutase and catalase, and ruxolitinib cream. Data availability for pre-specified outcomes of interest was low. Notably, F-VASI (the primary endpoint in the TRuE-V studies) and T-VASI were not reported in any study, other than TRuE-V1, TRuE-V2, and the Phase 2 clinical trial of ruxolitinib cream for the treatment of vitiligo (see **Table 22**). Considerable between-study heterogeneity was noted in terms of study design and patient population characteristics. Studies included in the FA featured various study designs, including RCTs (16/28), non-randomised clinical trials and single arm studies. High variability was observed in the geographies covered in the studies, including Europe, North America, Asia and Egypt. The sample size in 12 out of the 28 studies was ≥ 50 patients, ranging from 50 to 517 patients, whereas the remaining 16 studies had relatively small sample sizes ranging from 9 to 48 patients. A minority of RCTs and non-randomised clinical trials were associated

[1] Rothstein (2017) and Wu (2019) were excluded from the process prior to screening against the treatment characteristics since Rothstein (2017) was a proof-of-concept trial and Wu (2019) was a letter to the editor

with a low risk of bias, and the majority of single arm studies were of poor methodological quality.

With the exception of age and gender, baseline characteristics for potential effect modifiers were poorly reported across studies. To the extent evaluable, considerable between-study heterogeneity was observed for several population baseline characteristics, as illustrated by the following examples: participants of Hamzavi et al (98) had a much longer duration of disease compared with participants of other included studies. Hartmann et al (2005) (99) enrolled a far greater proportion of patients with Fitzpatrick skin type I-III compared with other included studies. In contrast, Sapam et al (100) and Bhatnagar et al (101) reported that 0% of participants had Fitzpatrick skin type I-III. Baseline VASI scores of participants in Anbar et al (102) were extremely low compared with other studies. The same study also enrolled a much lower proportion of male participants. In contrast to other studies, in Zhang et al (103) 100% of patients had stable disease at baseline. This study also reported an extremely low mean duration of disease (103).

Table 22. Data availability for outcomes of interest in studies with vitiligo

#	Author (Year)	Efficacy		Safety		PROs			Number of patients
		Change from basline (CFB) in VASI outcomes (Outcomes, timepoint)	CFB in BSA outcomes (Outcomes, Timepoint)	AEs with incidence ≥ 4%	Discontinuation due to AEs	CFB in DLQI (Timepoint)	CFB in VitiQoL (Timepoint)	VNS score 4/5 (Timepoint)	
1	Anbar (2019)	✓ (VASI, 24)	×	×	×	×	×	×	43
2	Baldo (2007)	×	×	×	✓	×	×	×	60
3	Baldo et al (2014)	×	×	×	✓	×	×	×	48
4	Bansal (2013)	✓ (VASI, 20)	×	✓	×	×	×	×	45
5	Bhatnagar (2007)	×	×	✓	×	×	×	×	50
6	Cavalie et al (2015)	×	×	✓	×	✓ (24)	×	×	35
7	Coskun et al (2005)	×	×	✓	×	×	×	×	10
8	Hamzavi (2004)	×	×	×	✓	×	×	×	22
9	Hartmann (2005)	×	×	×	×	✓(52)	×	×	9
10	Hartmann (2008)	×	×	✓	×	✓ (52)	×	×	31
11	Leone (2003)	×	×	✓	×	×	×		37
12	Lo (2010)	×	×	✓	×	×	×		61
13	Majid (2014)	×	×	✓	×	×	×	×	40
14	Mehrabi (2006)	×	×	✓	×	×	×	×	9
15	Paracha (2010)	×	×	✓	×	×	×	×	60
16	Rosmarin (2017)	×	✓ (BSA 20)	✓	×	✓ (20)	×	×	11
17	Rosmarin (2020)	✓ (T-VASI, 24)	✓(F-BSA, 24 & 52; T-BSA, 24 & 52)	✓	✓	×	×	×	157
18	Saleh et al (2021)	✓(VASI, 24)	×	×	×	×	×	×	63
19	Sanjana 2021	×	×	×	×	✓(24)	×	×	79
20	Sapam (2012)	×	×	✓	×	×	×	×	56
21	Seneschal (2021)	×	×	✓	✓	×	×	×	42
22	Siadat (2014)	×	×	✓	×	×	×	×	42
23	Singh et al (2013)	×	×	✓	×	×	×	×	35
24	Thomas (2021)	×	×	✓	×	×	×	✓(24)	517
25	TRuE-V1	✓ (T-/F-VASI, 24)	✓(F-BSA, 24)	✓	✓	✓(24)	✓ (24)	✓ (20)	330
26	TRuE-V2	✓ (T-/F-VASI, 24)	✓(F-BSA, 24)	✓	✓	✓(24)	✓ (24)	✓ (20)	344
27	Zhang et al (2019)	✓(VASI, 24)	×	×	×	×	✓ (24)	×	94
28	Zabolinejad (2020)	✓(VASI, 20)	×	✓	×	×	×	×	40

Abbreviations: AE, Adverse event; CFB, Change from baseline; DLQI, Dermatology Life Quality Index; PRO, Patient reported outcomes; T-BSA, Total Body Surface Area; T-VASI, Total body Vitiligo Area Scoring Index; VASI, Vitiligo Area Scoring Index VitiQoL, Vitiligo-specific quality-of-life; VNS, Vitiligo Noticeability Scale.
Note: Rows highlighted in blue refer to single arm trials.
Source: Incyte. Appendix D.

B2.9.3 ITC conclusions

The ITC FA found that there is an insufficient evidence base to robustly compare the efficacy of ruxolitinib cream to existing off-label therapies. The lack of comparable studies is partly due to an evolving set of tools that are used to evaluate vitiligo. In addition, most of the clinical studies were of low methodological quality.

B.2.10 Adverse reactions

Overall, ruxolitinib cream demonstrated long-term tolerability in TRuE-V1 and TRuE-V2. In adults and adolescents, 79.2% (n = 350/442) of patients who were randomised to receive ruxolitinib cream remained on active therapy after 52 weeks of treatment; see

Figure *6* (2, 3, 94).

Ruxolitinib cream demonstrated low systemic exposure, with fewer than 2% experiencing one or more plasma ruxolitinib concentrations above the whole blood half-maximal inhibitory concentration (IC50) for JAK2 inhibition, which is considered a clinically relevant threshold value for encountering JAK-related side effects associated with ruxolitinib cream. Further, there is no evidence of elevated major adverse cardiovascular events (MACE), venous thromboembolism (VTE), malignancy or serious infections with ruxolitinib cream (2, 3).

The primary analysis of safety was based on pooled data from the double-blind period in the Phase 3 confirmatory studies in patients with vitiligo (TRuE-V1 and TRuE-V2) **(94, 95)**. These 2 identically designed, randomised, double-blind, vehicle-controlled studies enrolled a total of 673 patients with vitiligo who applied ruxolitinib cream (449 patients) or vehicle cream (224 patients) in a blinded manner for 24 weeks (2, 3).

B.2.10.1.1 TRuE-V1 and TRuE-V2 – overall summary of adverse events

The overall incidence of (all-cause) treatment-emergent adverse events (TEAEs) and treatment-related TEAEs was higher in the ruxolitinib cream group (47.7% and 14.7%, respectively) versus the vehicle cream treatment group (35.3% and 7.6%, respectively (see **Table 23**) (2, 3, 94, 95). This was primarily driven by a higher incidence of application site reactions (ASRs) in patients in the ruxolitinib cream group compared to vehicle (14.9% vs 5.8%) (94, 95). When adjusted for exposure, the incidence rates (IRs) of TEAEs were lower in patients who applied ruxolitinib cream than in patients

who applied vehicle cream (62.8 vs 91.9 per 100 person-years [PY] and 77.3 vs 72.3 per 100 PY in TRuE-V1 and TRuE-V2, respectively) (95). Few patients had Grade 3 or higher TEAEs, serious TEAEs, or TEAEs leading to study drug discontinuation or interruption, and no patient had a TEAE with a fatal outcome (2, 3, 94, 95).

Table 23. Overall summary of treatment-emergent adverse events (pooled population) (2, 3)

Category, n (%)	Vehicle cream (N = 224)	Ruxolitinib cream (N = 449)
Patients who had a TEAE	79 (35.3)	214 (47.7)
Patients who had a treatment-related TEAE	17 (7.6)	66 (14.7)
Patients who had a Grade 3 or higher severity TEAE	4 (1.8)	10 (2.2)
Patients who had a treatment-related Grade 3 or higher severity TEAE	0	0
Patients who had a serious TEAE	1 (0.4)	8 (1.8)
Patients who had a treatment-related serious TEAE	0	0
Patients who had a TEAE with a fatal outcome	0	0
Patients who had an ASR	13 (5.8)	67 (14.9)
Patients who had a TEAE leading to study drug interruption	4 (1.8)	6 (1.3)
Patients who had a TEAE leading to study drug discontinuation	1 (0.4)	2 (0.4)

Note: Participants from study site 710 in the TRuE-V2 study are included in this summary.
Abbreviations: ASR, application site reaction; TEAE, treatment emergent adverse events.
Source: Opzelura assessment report (EMA/135534/2023) (94).

B.2.10.1.2 TRuE-V1 and TRuE-V2 – treatment-emergent adverse events

TEAEs were most frequently reported in the following: infections and infestations (21.8% in the ruxolitinib cream group vs 16.5% in the vehicle cream group), general disorders and administration site conditions (16.5% vs 6.7%, respectively), gastrointestinal disorders (5.3% vs 2.7%, respectively), and skin and subcutaneous tissue disorders (4.2% vs 5.4%, respectively). Within each of these, TEAEs were largely Grade 1 or 2 in severity and nonserious. Further, TEAEs were more frequently reported in the ruxolitinib cream group as compared to the vehicle cream treatment group, in the following: investigations (4.7% vs 1.8%, respectively), respiratory disorders (3.3% vs 1.8%, respectively) (2, 3, 93-95, 104).

TEAEs occurring in ≥ 1% of patients in any treatment group are summarised in **Table 24** (2, 3, 94, 95). Application site acne was the most common TEAE among patients who applied ruxolitinib cream and was reported in more patients treated with ruxolitinib cream than vehicle cream (5.8% in the ruxolitinib cream group vs 0.9% in the vehicle cream treatment group. Other common TEAEs in patients in the ruxolitinib cream group (≥ 2%) included application site pruritus, nasopharyngitis, headache, COVID-19, upper respiratory tract infection, and sinusitis; of these other common events, application site pruritus and nasopharyngitis were reported more frequently for the ruxolitinib cream group compared with the vehicle cream treatment group (≥ 2.0% higher incidence). Other TEAEs were reported at similar incidences across both treatment groups (2, 3, 94, 95).

Table 24. Summary of treatment-emergent adverse events occurring in ≥ 1% of patients in any treatment group (Phase 3 pooled population) (2, 3)

MedDRA PT, n (%)	Vehicle cream (N = 224)	Ruxolitinib cream (N = 449)
Patients with any TEAE	*79 (35.3)*	*214 (47.7)*
Application site acne	2 (0.9)	26 (5.8)
Application site pruritus	6 (2.7)	23 (5.1)
Nasopharyngitis	5 (2.2)	19 (4.2)
Headache	6 (2.7)	17 (3.8)
COVID-19	6 (2.7)	13 (2.9)
Upper respiratory tract infection	5 (2.2)	13 (2.9)
Sinusitis	5 (2.2)	10 (2.2)
Application site erythema	1 (0.4)	7 (1.6)
Application site rash	2 (0.9)	7 (1.6)
Influenza	1 (0.4)	6 (1.3)
Pyrexia	0	6 (1.3)
Urinary tract infection	1 (0.4)	6 (1.3)
Alanine aminotransferase increased	1 (0.4)	5 (1.1)
Oral herpes	3 (1.3)	5 (1.1)
Arthralgia	3 (1.3)	3 (0.7)
Pharyngitis streptococcal	3 (1.3)	0

Note: Participants from study site 710 in the TRuE-V2 study are included in this summary.
Abbreviations: COVID-19, coronavirus disease 2019; MeDRA, medical dictionary for regulatory activities; PT, preferred terms; TEAE, treatment emergent adverse events.
Source: Opzelura assessment report (EMA/135534/2023) (94)

B.2.10.1.3 *TRuE-V1 and TRuE-V2* – serious adverse events

Table 25 presents serious TEAEs in the Phase 3 vitiligo vehicle-controlled population. No serious TEAEs occurred in > 1 patient in any treatment group, and no serious TEAE was considered related to the study drug by the investigator (2, 3, 93-95). The Grade 3 coronary artery stenosis occurred in a 57-year-old patient who was overweight (BMI: 29.6 kg/m^2) and had a history of hyperlipidemia and hypertension and a family history of cardiac disease (95).

Table 25. Summary of serious treatment-emergent adverse events (pooled population) (2, 3)

MedDRA PT, n (%)	Vehicle cream (N = 224)	Ruxolitinib cream (N = 449)
Patients with any serious TEAE	*1 (0.4)*	*8 (1.8)*
Anal fistula	0	1 (0.2)
Appendicitis	0	1 (0.2)
Concussion	0	1 (0.2)
Coronary artery stenosis	0	1 (0.2)
Hepatitis infectious mononucleosis	0	1 (0.2)
Kidney contusion	0	1 (0.2)
Myocarditis	0	1 (0.2)
Ureterolithiasis	0	1 (0.2)
Tibia fracture	1 (0.4)	0

Note: Participants from study site 710 in the TRuE-V2 study are included in this summary.
Abbreviations: MeDRA, medical dictionary for regulatory activities; PT, preferred terms; TEAE, treatment emergent adverse events.
Source: Opzelura assessment report (EMA/135534/2023) (94).

B.2.10.2.1 *TRuE-V LTE – overall summary of adverse events*

An overall summary of TEAEs for patients in Cohort A is presented in **Table 26** (4). The results demonstrate that continued treatment with ruxolitinib cream for up to 104 weeks was safe and well-tolerated. Few patients in Cohort A had Grade 3 or higher TEAEs, serious TEAEs, or TEAEs leading to dose reduction, and no patient had a TEAE with a fatal outcome or a TEAE leading to study drug discontinuation (4).

The overall incidences of TEAEs (all causality) and ASRs for Cohort A were higher among patients who applied ruxolitinib cream (43.2% and 6.2%, respectively) compared with the vehicle cream treatment group (36.2% and 3.4%, respectively; see **Table 26**) (4). When adjusted for exposure, the IR of TEAEs was higher in patients who applied vehicle cream (60.2 per 100 PY) than in patients who applied ruxolitinib cream (50.6 per 100 PY), while the IR of ASRs was similar in patients who applied ruxolitinib cream (7.2 per 100 PY) compared with vehicle cream (5.7 per 100 PY) (4).

Table 26. Overall Summary of Treatment-Emergent Adverse Events (FAS: Cohort A) (4)

Category, n (%)	Vehicle cream (N = 58)	Vehicle cream to Ruxolitinib cream (N = 23)	Ruxolitinib cream (N = 58)	Ruxolitinib cream Total (N = 81)
Patients who had a TEAE	21 (36.2)	3 (13.0)	32 (55.2)	35 (43.2)
Patients who had a treatment-related TEAE	3 (5.2)	0 (0.0)	3 (5.2)	3 (3.7)
Patients who had a serious TEAE	0 (0.0)	0 (0.0)	1 (1.7)	1 (1.2)
Patients who had a Grade 3 or higher TEAE	1 (1.7)	0 (0.0)	1 (1.7)	1 (1.2)
Patients who had a fatal TEAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patients who had an ASR	2 (3.4)	1 (4.3)	4 (6.9)	5 (6.2)
Patients who had a TEAE leading to study drug discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patients who had a TEAE leading to dose reduction[a]	0 (0.0)	0 (0.0)	1 (1.7)	1 (1.2)
Patients who had a TEAE leading to study drug interruption	0 (0.0)	0 (0.0)	1 (1.7)	1 (1.2)
Patients who had a Grade 3 or higher treatment-related TEAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patients who had a treatment-related serious TEAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: ASR, application site reaction; FAS, full analysis set; TEAE, treatment emergent adverse event.
Source: INCB 18424-308 (TRuE-V LTE) Clinical Study Report (4).
[a] One patient had application site dermatitis (verbatim: contact dermatitis) and stopped applying study drug at the site of the irritation. This was recorded as a dose reduction, although dose reductions were not allowed per protocol.

An overall summary of TEAEs for patients in Cohort B is presented in **Table 27** (4). The results demonstrate that ruxolitinib cream was safe and well-tolerated when administered for up to 104 weeks. The incidences of serious TEAEs (3.2%) and Grade 3 or higher TEAEs (4.1%) were low, few patients had TEAEs leading to changes to the study drug (i,e,. study drug interruption [1.2%], reduction [0.6%], or discontinuation [0.3%]), and no patient had a TEAE with a fatal outcome (4).

The incidences of TEAEs (all causality) and ASRs for patients in Cohort B were similar for patients initially randomised to ruxolitinib cream (i.e., patients who entered the study with 52 weeks of ruxolitinib cream) and those initially randomised to vehicle cream (i.e., patients who entered the study with 28 weeks of treatment with ruxolitinib

cream). Overall, approximately half of patients (50.6%) had a TEAE, and 7.3% of patients had at least 1 ASR (4).

Table 27. Overall Summary of Treatment-Emergent Adverse Events (FAS: Cohort B) (4)

Category, n (%)	Vehicle cream to Ruxolitinib cream (N = 118)	Ruxolitinib cream to Ruxolitinib cream (N = 224)	Total (N = 342)
Patients who had a TEAE	59 (50.0)	114 (50.9)	173 (50.6)
Patients who had a treatment-related TEAE	6 (5.1)	14 (6.3)	20 (5.8)
Patients who had a serious TEAE	4 (3.4)	7 (3.1)	11 (3.2)
Patients who had a Grade 3 or higher TEAE	5 (4.2)	9 (4.0)	14 (4.1)
Patients who had a fatal TEAE	0 (0.0)	0 (0.0)	0 (0.0)
Patients who had an ASR	6 (5.1)	19 (8.5)	25 (7.3)
Patients who had a TEAE leading to study drug discontinuation	1 (0.8)	0 (0.0)	1 (0.3)
Patients who had a TEAE leading to dose reduction[a]	1 (0.8)	1 (0.4)	2 (0.6)
Patients who had a TEAE leading to study drug interruption	2 (1.7)	2 (0.9)	4 (1.2)
Patients who had a Grade 3 or higher treatment-related TEAE	0 (0.0)	0 (0.0)	0 (0.0)
Patients who had a treatment-related serious TEAE	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: ASR, application site reaction; FAS, full analysis set; TEAE, treatment emergent adverse event.
Source: INCB 18424-308 (TRuE-V LTE) Clinical Study Report (4).
[a] One patient had application site dermatitis (on the forehead and perioral) and application site acne on the face, and 1 patient had application site eczema (verbatim: dyshydrosis); both patients stopped applying study drug at the site of the irritation. This was recorded as a dose reduction, although dose reductions were not allowed per protocol.
Note: The treatment group is based on the actual treatment applied in the parent studies.

B.2.11 Ongoing studies

There are no ongoing studies of relevance to be reported in this submission.

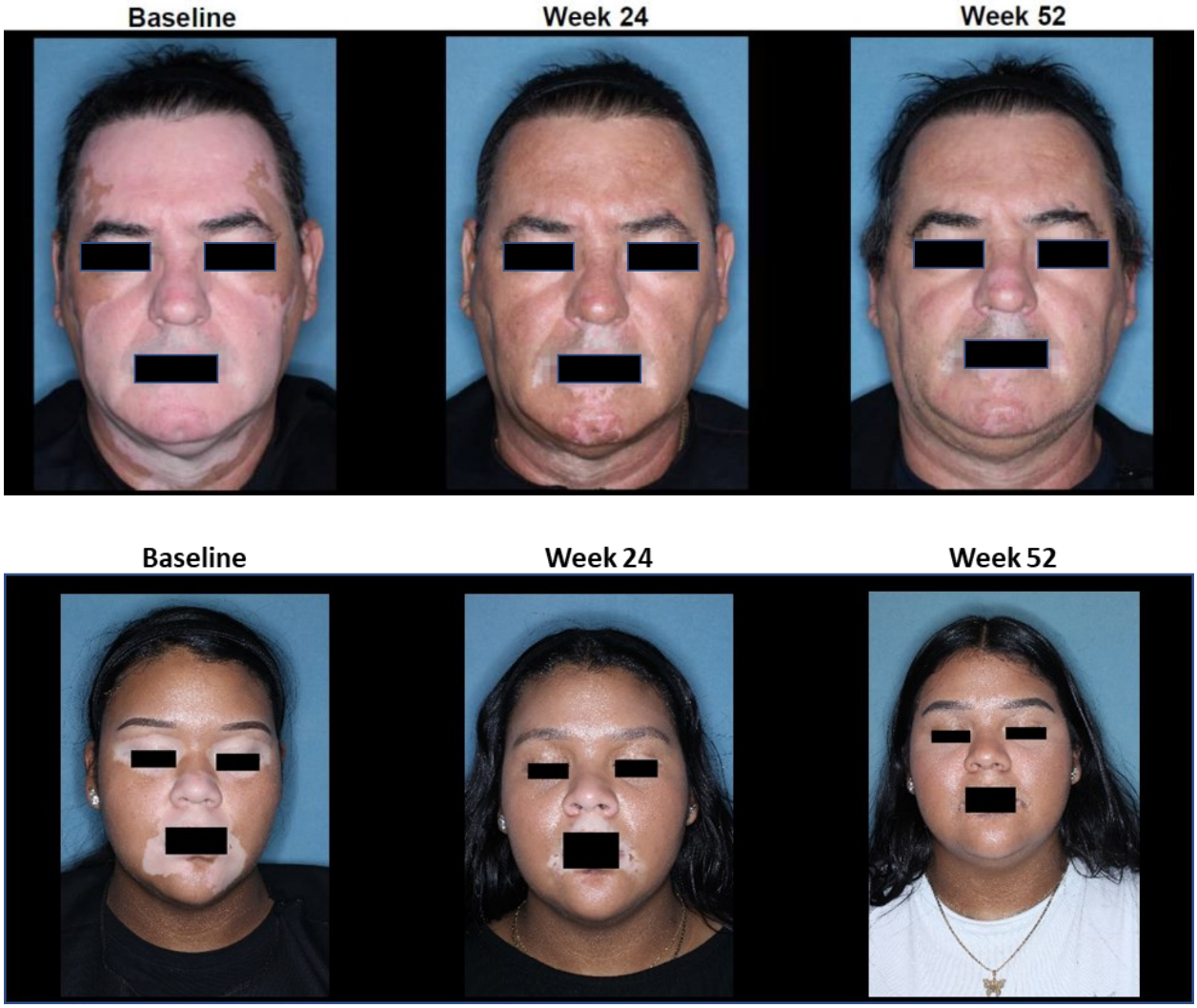
B.2.12 Interpretation of clinical effectiveness and safety evidence

Patients impacted by NSV with facial involvement who currently have to manage their disease without licensed treatments experience a high unmet need for effective treatments which target the cause of their condition and reduce the psychosocial burden, thereby improving QoL.

Ruxolitinib cream is the first treatment to be approved specifically for NSV with facial involvement. It halts depigmentation and enables re-pigmentation to natural skin

colour via an anti-inflammatory mode of action that also facilitates endogenous repigmentation of lesions (**Figure 19**). Ruxolitinib cream has been studied in two Phase III double-blind RCTs (TRuE-V1 and 2) and a Phase III trial double-blind, vehicle-controlled, randomised withdrawal and treatment extension study enrolling patients who completed TRuE-V1 and 2, using a validated instrument (F-VASI75) as the primary endpoint (90-92).

Figure 19. Patients who achieved F-VASI90 in the TRuE-V studies (105)



Source: Incyte. Clinical photos and associated scores of patients in the TRuE-V studies [Data on file] (105).

B.2.12.1 Clinical effectiveness

Overall, ruxolitinib cream was associated with favourable outcomes in the vast majority of endpoints in the TRuE-V trials, including F-VASI75, F-VASI90, F-VASI50, T-VASI50, VNS 4 or 5, and HADS scores for depression and anxiety (2-4, 94, 97).

At Week 24, approximately one in three patients achieved at least 75% improvement in facial re-pigmentation with ruxolitinib cream, approximately three times more than with vehicle cream (30.7% vs 9.6% [OR = 4.17; p < 0.0001]). F-VASI75 responses continued to improve at Week 52 (50.3% vs 28.2%), and were irrespective of facial lesion size. The 75% repigmentation of the skin of the face is considered a clinically relevant magnitude of change, and this was supported by treatment effects seen in the patient-reported VNS. Data beyond week 24 confirm further improvement of treatment response (rates) between weeks 24 and 52 (94).

The majority of patients who had achieved complete or near-complete repigmentation of the face (≥ F-VASI90 at Week 52) did not experience relapse (< F-VASI75) while on study; 69.1% and 39.3% of patients in the ruxolitinib cream and vehicle cream treatment groups, respectively, did not experience relapse through Week 104, and 12.7% and 23.2%, respectively, had not experienced relapse at the time of early discontinuation from study cream. The majority of patients who had achieved ≥ F-VASI90 at Week 52 maintained this level of repigmentation with continued ruxolitinib cream application beyond Week 52; 61.8% of patients had not lost their F-VASI90 response through Week 104, and 10.9% had not lost their F-VASI90 response at the time of early discontinuation from study cream (4). While some patients randomised to ruxolitinib cream in Cohort A experienced relapse, the majority (5 of 8 patients [62.5%]) regained F-VASI75 with continued application of ruxolitinib cream; the median time to regain F-VASI75 was 205.0 days (95% CI: 0.109, 1.439) (4).

Improvements were also observed in non-facial areas (94). At Week 24, 21.9% of patients reached at least 50% repigmentation of the total body with ruxolitinib cream, compared with 5.8% in the vehicle group, with a response rate difference of 16.1% (p

< 0.0001). T-VASI50 responses continued to improve at Week 52 (51.1% vs 27%) (94).

B.2.12.2 Safety

Ruxolitinib cream demonstrated long-term tolerability in two Phase III double-blind RCTs. In adults and adolescents, 79.2% (n = 350/442) of patients remained on active therapy after 52 weeks of treatment (2, 3, 94). When adjusted for exposure, incidence rates for treatment-emergent adverse events were lower with ruxolitinib cream than with vehicle cream (62.8 vs 91.9 per 100 PY and 77.3 vs 72.3 per 100 PY in TRuE-V1 and TRuE-V2, respectively) (95). Few patients had Grade 3 or higher TEAEs, serious TEAEs, or TEAEs leading to study drug discontinuation or interruption, and no patient had a TEAE with a fatal outcome (2, 3, 94, 95).

Ruxolitinib cream demonstrated low systemic exposure, with fewer than 2% of patients experiencing plasma concentrations at the level associated with risk of JAK-related adverse events (2, 3). There is no evidence of elevated MACE, VTE, malignancy or serious infections with ruxolitinib cream (106).

Results from the long-term extension study (TRuE-V LTE) demonstrated that continued treatment with ruxolitinib cream for up to 104 weeks was safe and well-tolerated. Few patients in Cohort A had Grade 3 or higher TEAEs, serious TEAEs, or TEAEs leading to dose reduction, or drug discontinuation, and no patient had a TEAE with a fatal outcome (4).

B.2.12.3 Strengths, limitations and the validity of study results

Strengths

The clinical evidence is based on two randomised Phase 3 trials and an open-label long-term extension study with robust designs (90-92). The TRuE-V clinical trials are the largest randomised clinical trials for vitiligo globally, including more than 600 adolescent and adult patients aged 12 years and older with NSV (2, 3).

Data from these studies capture evidence on clinically relevant outcomes in this disease, including facial repigmentation as the primary endpoint (2, 3). The selected

trial endpoints provide important insights that are relevant to real-world practice and clinical decision making.

The TRuE-V trials were conducted in centres in Europe and North America and the patients enrolled reflect the target population i.e., patients with NSV vitiligo with facial involvement (2, 3), therefore, the clinical evidence is generalisable to the UK setting. Furthermore, the outcomes that were measured in the TRuE-V clinical trials are reflective of the core outcome sets that are recommended for vitiligo clinical trials (107).

Limitations

Direct comparison of efficacy and safety of ruxolitinib cream versus off-label treatments such as TCS, TCI and phototherapy is not feasible in a multinational clinical setting, and blinding is not feasible versus phototherapy. Further, there are numerous safety concerns associated with the use of other prescription therapies for vitiligo, including a risk of treatment-related serious adverse effects (8, 9, 15, 108). As per the Helsinki declaration, there are ethical concerns associated with performing a clinical trial with a comparator known to carry a significant risk of additional and/or irreversible health risks (109).

A limitation in the parent TRuE-V1 and TRuE-V2 studies is that comparison between ruxolitinib cream and vehicle cream was limited to the first 24 weeks of double-blind treatment, however, this was considered the longest acceptable duration of no active treatment (vehicle) and the minimum time required to observe a meaningful clinical response to treatment, making it suitable for the assessment of the primary endpoint in these studies (2, 3).

In addition, the two Phase 3 trials were conducted during the COVID-19 pandemic, which may have contributed to patients being lost to follow-up. In order to minimise potential bias from missing values and the impact on study interpretation, multiple imputation was used to replace NRI as the primary method for handling missing values in the analyses of the primary and key secondary endpoints (94).

Most enrolled patients in the TRuE-V studies were white and had skin types I, II, or III (2, 3, 94). Although generalisation to patients with darker skin types is limited on the basis of patient enrolment, subgroup analyses of Phase 3 data indicated that incidence of repigmentation response may be similar among patients with fairer skin and those

with darker skin (2, 3, 94). However, the impact on quality of life will likely be more prominent in patients with darker skin (74).

More patients with fairer skin were enrolled in the TRuE-V studies (2, 3) in comparison with the Home Interventions and Light Therapy for the treatment of vitiligo (HI-Light) study (110). HI-Light is a UK National Institute for Health and Care Research (NIHR)-sponsored pragmatic RCT that evaluated the effectiveness of home-based light therapy and TCS cream, used alone or in combination, for the treatment of vitiligo (110). As the impact of vitiligo on QoL is more prominent in patients with darker skin, the QoL outcomes that were measured in the TRuE-V studies were likely underestimated.

Substantial heterogeneity exists between studies conducted on patients with vitiligo. This is caused by the lack of specific standardised outcomes for vitiligo prior to the design of the TRuE-V clinical development programme, which created challenges in stratifying the severity of vitiligo. Incyte conducted an ITC FA which found that there is an insufficient evidence base to robustly compare the efficacy of ruxolitinib cream to existing off-label therapies (**Appendix D**).

Validity of study results

A quality assessment was conducted, the results of which revealed no major concerns regarding potential sources of bias (**Appendix D**). The trials were designed and conducted appropriately with regards to randomisation and treatment allocation. Patients were similar between treatment groups prior to randomisation with no major imbalances.

VASI is a reliable and responsive instrument to assess the degree of depigmentation in vitiligo patients (104, 111). Results from psychometric analysis that was conducted to evaluate the psychometric properties of the F-VASI and T-VASI in adolescents and adults with NSV indicate that F-VASI and T-VASI instruments are reliable, valid, and responsive to change, with defined clinically meaningful within-patient change in adolescents and adults with NSV with depigmented areas ≤10% total BSA (facial and non-facial) with ≥0.5% facial BSA and ≥3% non-facial BSA (46, 47). The meaningful change threshold analysis revealed that an appropriate individual level threshold for identifying clinically relevant responders would be between 0.38 to 0.60 for F-VASI, and between 1.69 and 3.88 for T-VASI (46, 47).

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

An economic SLR was conducted to identify any relevant economic evaluations for the treatment of vitiligo and healthcare resource use (HCRU), details of which are provided in Appendix G. The original SLR was performed in February 2022 and updated in January 2023 to identify previously published cost-effectiveness analysis (CEA) studies to inform the model development and to capture HCRU data in adolescent and adult patients with vitiligo. Searches were conducted in the MEDLINE, Embase, and EBM Reviews databases, with an additional search of recently published abstracts from six conferences including International Society for Pharmacoeconomics and Outcomes Research (ISPOR).

Two similar studies reporting cost-effectiveness were identified (**Table 28**), both based on the same 9-month analytic model developed using results from the HI-Light clinical trial. Sach et al. (2021) (112) conducted a cost-effectiveness analysis alongside the HI-Light Vitiligo Trial to determine the cost-effectiveness of (i) handheld NB-UVB and (ii) a combination of TCS and NB-UVB, compared with TCS alone. Batchelor et al. (2020) (82) conducted a similar analysis published as a Health Technology Assessment. Both studies were deemed relevant to the decision problem and their HCRU data were used to inform model inputs. However, given that these studies conducted a within-trial (i.e., non-model-based) analysis, conceptual modelling approaches for the current appraisal were sourced from elsewhere, as described below in Section B.3.2.2 Model structure.

Table 28. Summary of relevant cost-effectiveness studies

Study		Sach et al. (2021) (112)	Batchelor et al. (2020) (82)
Year		2021	2020
Type of economic analysis		CEA/CUA	CEA/CUA
Intervention vs comparator		NB-UVB vs TCS & NB-UVB + TCS vs TCS	NB-UVB vs TCS & NB-UVB + TCS vs TCS
Time horizon		9 months	9 months
Perspective		NHS and personal	NHS and family
Patient population; mean age (SD)		37.0 (19.1)	37.5 (19.3)
Clinical Data Source		HI-Light Vitiligo Trial (110) Haines et al, 2018 & Batchelor et al, 2016 (113, 114)	HI-Light Vitiligo Trial (110) Haines et al, 2018 & Batchelor et al, 2016 (113, 114)
HRQoL inputs		EQ-5D-5L; CHU-9D	EQ-5D-5L; CHU-9D
QALYs	CUA (Utility for EQ 5D-5L aged ≥ 11 years)	NB-UVB: 0.6871 NB-UVB + TCS: 0.6843 TCS: 0.6721	NB-UVB: 0.6871 NB-UVB + TCS: 0.6843 TCS: 0.6721
	CUA (Utility for CHU-9D for those aged < 18 years)	NB-UVB: 0.7154 NB-UVB + TCS: 0.6988 TCS: 0.7135	NB-UVB: 0.7154 NB-UVB + TCS: 0.6988 TCS: 0.7135
Costs (GBP, 2017) (Intervention)	CUA (Utility for EQ 5D-5L aged ≥ 11 years)	NB-UVB: £775 NB-UVB + TCS: £813 TCS: £600	NB-UVB: £774.64 NB-UVB + TCS: £813.38 TCS: £599.99
	CUA (Utility for CHU-9D for those aged < 18 years)	NB-UVB: £775 NB-UVB + TCS: £813 TCS: £600	NB-UVB: £818.47 NB-UVB + TCS: £818.47 TCS: £597.51

ICER (per QALY gained)	CUA (Utility for EQ 5D-5L aged ≥ 11 years)	NB-UVB vs TCS: £8293.88 NB-UVB + TCS vs TCS: £14081	NB-UVB vs TCS: £8293.88 NB-UVB + TCS vs TCS: £14081
	CUA (Utility for CHU-9D for those aged < 18 years)	NB-UVB vs TCS: £92381.98 TCS: TCS Dominates NB-UVB + TCS	NB-UVB vs TCS: £92381.98 TCS: TCS Dominates NB-UVB + TCS

Abbreviations: CEA, Cost-Effectiveness Analysis; CHU-9D, Child Health Utility; CUA, Cost-Utility Analysis; EQ-5D-5L, EuroQoL-5 Dimension-5 Level questionnaire; GBP, British pound sterling; HRQoL, Health Related Quality of Life; ICER, Incremental Cost Effectiveness Ratio; N/A, Non-applicable; NB-UVB, Narrow-band ultraviolet B; NHS: National Health Service; NR, Not Reported; SD, Standard Deviation; TCS, Topical Corticosteroid; QALYs, Quality Adjusted Life Years.

B.3.2 Economic analysis

In line with the decision problem for this submission, the objective of this economic analysis was to assess the cost-effectiveness of ruxolitinib cream compared with vehicle cream for the treatment of patients with NSV with facial involvement. As no previously published model-based cost-effectiveness analyses in vitiligo were identified in the SLR (Section B.3.1 Published cost-effectiveness studies), a review of previous NICE submissions in other dermatological indications alongside extensive expert validation meetings informed the modelling approach.

A *de novo* model was developed in Microsoft® Excel using a Markov approach to capture the key features and natural history of vitiligo, the design of the TRuE-V trials, and the current clinical pathway of care for the patient population of interest in England.

In line with the NICE reference case (115), the analysis was conducted from the cost perspective of the NHS and Personal Social Services (PSS) and in accordance with the NICE methods manual for technology appraisals (116).

B.3.2.1 Patient population

The marketing authorisation for ruxolitinib cream (granted on 4th July 2023) is for the treatment of NSV with facial involvement in adults and adolescents from 12 years of age (19). The economic analysis addresses a sub-population of the licensed population (as mentioned in section B.1.1), that is, for patients whose disease has not responded to TCS or TCI, or for whom TCS or TCI are contraindicated, not tolerated or otherwise medically inadvisable. The analysis, conducted using the pooled data from two identical Phase III trials, TRuE-V1 and TRuE-V2 (2, 3) and data from the TRuE-V LTE study (4) is broadly consistent with the final scope issued by NICE, however, now reflects a narrower target population for ruxolitinib cream. This revised positioning addresses the highest unmet need for vitiligo patients in England and is more relevant to NHS clinical practice (89).

B.3.2.2 Model structure

Given the aforementioned lack of published model-based cost-effectiveness analyses in vitiligo, a review of previous NICE submissions in other dermatological conditions was carried out to inform the development of a model for vitiligo. Two earlier appraisals in atopic dermatitis (AD; TA534 and TA681) (117, 118) and two in psoriasis (TA146

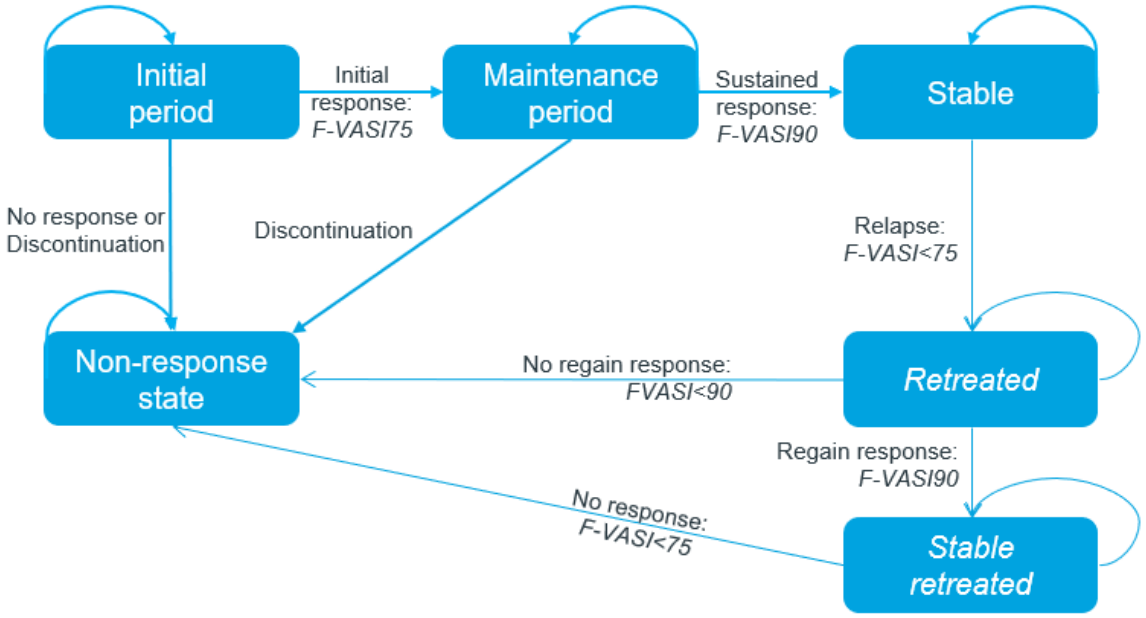
and TA574) (119, 120) were identified. These appraisals included either a Markov model (TA681 and TA574) or a decision tree combined with a Markov trace (TA534 and TA146). Due to the chronic nature of vitiligo, a Markov modelling approach was also deemed appropriate for the current economic evaluation.

These submissions were reviewed with extensive validation meetings with clinical and health economic experts. Three clinical experts specialising in dermatology and one health economic expert were consulted as part of the development of the model structure (121).

The clinical experts advised that a typical patient who is being treated for their vitiligo would undergo a response assessment following an initial course of treatment. If a response is observed, treatment would then continue until a plateau in repigmentation is observed, at which point treatment would stop as the patient would be considered to have reached a stable state. It was also noted by the clinicians that in clinical practice, patients who had a loss of response (i.e., experienced depigmentation) after an initial response to therapy (i.e., experiencing regimentation) may be retreated to regain response (i.e., repigmentation levels returning to repigmentation noted in the previous stable state).

This clinical treatment pathway is reflected in the model structure given in **Figure 20**, which builds on the model submitted as part of TA681 to account for a 'stable' state and re-treatment. The three clinical experts unanimously confirmed that the model structure is a valid representation of the chronic nature of vitiligo and reflects the clinical treatment pathway in England. In addition, the health economic expert confirmed that the model structure is appropriate to capture this care pathway. A full description of the model is given in the subsequent paragraphs below.

Figure 20. Model structure



Note: Dead, not presented in the figure for simplicity, is an absorbing state and can be reached from any of the other health states

Table 29 provides a summary of the allowed transitions in the model and their respective definitions.

Table 29. Summary of allowed model transitions

Model Transitions	Description
Initial period → Maintenance period	Transition defined by achievement of an initial response to treatment (i.e., F-VASI75)
Maintenance period → Stable	Transition defined by achievement of a sustained response to treatment (i.e., F-VASI90)
Stable → Re-treated	Transition defined by F-VASI<75 (i.e., when F-VASI drops below 75), the definition of a relapse
Re-treated → Stable retreated	Transition defined by re-achievement of F-VASI90 after retreatment
Movements to non-response	Patients may transition to the non-response state following either • No achievement of initial response to treatment (F-VASI<75) • Discontinuation from the initial or maintenance periods, respectively • No response regained following retreatment (F-VASI<90) or • A loss of response (F-VASI<75) following achievement of F-VASI90 after retreatment
Movements to death	Patients may transition to 'dead' from any health state

Abbreviations: F-VASI, facial vitiligo area scoring index; F-VASI75, 75% or greater improvement from baseline in F-VASI; F-VASI90, 90% or greater improvement from baseline in F-VASI.

The model was developed to reflect how patients would be treated and assessed in clinical practice. Upon entering the model, patients are allocated to ruxolitinib cream or vehicle cream and enter the initial period health state. Patients remain in this health state for a maximum of 24 weeks, when the response to initial treatment is assessed, unless the treatment is discontinued due to any causes excluding efficacy. Week 24 was chosen as the timepoint for assessment of initial response as it aligns with the duration of the double-blind period of the TRuE-V studies (except for discontinuation due to all causes excluding efficacy). This timepoint of 24 weeks for assessment of initial response was confirmed by the dermatologists to be aligned with clinical practice (122). Initial response is defined as F-VASI75 (i.e., indicating an at least 75% improvement from baseline F-VASI score) consistent with the primary endpoint of the TRuE-V1 and TRuE-V2 trials (93) (Section B.2.1 Identification and selection of relevant studies) and validated by clinicians as a suitable measure of response (122). Importantly, F-VASI75 has been validated by patients as being indicative of treatment success (123).

Patients who respond based on having achieved an initial response of F-VASI75 would, in clinical practice, continue to receive treatment. As such, they are modelled as transitioning to the maintenance period health state where they continue treatment with either ruxolitinib cream or vehicle cream. Patients who have not responded (i.e., F-VASI<75; non-responders) discontinue treatment with ruxolitinib cream or vehicle cream and are modelled as transitioning to the non-response health state to receive subsequent best supportive care (BSC), consistent with UK clinical practice.

Patients continuing treatment with ruxolitinib cream (i.e., those who are in the maintenance period) are assessed for a sustained response following a further 28 weeks of treatment (i.e., 52 weeks in total) in alignment with the treatment extension period of the TRuE-V studies (2-4).

Sustained response is defined as F-VASI90 (indicating at least 90% improvement from baseline F-VASI score), which was deemed a clinically plausible definition of sustained response as part of the validation meetings described above. This definition is also aligned with the eligibility criteria of Cohort A in the TRuE-V LTE study (Section B.2.6.2 *Withdrawal and treatment extension study (TRuE-V LTE)*) (4).

Patients who achieve a sustained response at week 52 are considered stable and are modelled as transitioning to the stable health state where they no longer receive treatment, as validated by clinicians (122). Patients who do not achieve F-VASI90 (i.e., non-responders) as part of the sustained response assessment at week 52 continue to receive treatment. They are assessed for response (i.e., F-VASI90) at four-weekly intervals following the 52-week assessment when they may also transition to the stable health state and stop treatment or transition to the non-response state.

All patients defined as not responding following either the initial or the maintenance assessment periods as well as the four-weekly assessment intervals discontinue treatment and, as validated by clinicians, subsequently receive BSC (122). Patients who discontinue for any other reasons also receive BSC; both are modelled as transitioning to the non-response state.

Clinicians described that patients in stable state may experience loss of response (i.e., depigmentation), in which case they would be considered for retreatment (122). To accurately reflect this feature of clinical practice, the model incorporates 'retreated' and 'stable state following retreatment (stable retreated)' health states. Patients in the stable health state who experience a relapse are retreated. This is modelled by patient transitions to the re-treated health state. This is in line with clinical advice and also reflects the design of the TRuE-V LTE where all randomised patients received ruxolitinib cream following a relapse (Section B.2.6.2 *Withdrawal and treatment extension study (TRuE-V LTE)* (122). As such a relapse rate is applied to the modelled stable patients, which is informed by the proportion of patients whose response level dropped below F-VASI75, in line with the definition of relapse in Cohort A of the TRuE-V LTE study (Section B.2.6.2.1 *Primary endpoint: Time to relapse (< F-VASI75)*) (4), and is considered every four weeks. This definition of relapse was validated by clinicians (122) and defines movement to the retreated health state.

As expected in clinical practice, and highlighted by the TRuE-V LTE study (Section B.2.6.2 *Withdrawal and treatment extension study (TRuE-V LTE)*), patients being retreated can regain their original response and are considered stable again (4, 122). The same response definition as the transition from the maintenance period to stable health state (i.e., F-VASI90) is used to model patients regaining their response and thereby transitioning to the 'stable retreated' health state. The 'regain response'

transition from the re-treated to the stable retreated health states is based on the time to regain F-VASI90 response data for participants on vehicle cream in Cohort A of the TRuE-V LTE study (4). Vehicle cream data are used as patients in the stable health state are modelled as not receiving treatment. The model assumes that patients will only be retreated once (due to data limitations), input from clinical experts confirmed that retreatment following relapse would be considered in patients that initially responded to treatment, but stopped due to lack of response (122). It is assumed that no patients discontinue treatment whilst being retreated.

As per clinical validation, patients are considered stable (and therefore are modelled as remaining in the retreated health state) until they lose response, upon which they transition to the non-response state and receive BSC (122). The transition from the stable retreated health state to non-response is informed by a response definition of < F-VASI75, identical to the definition of relapse described above and with the same data as that used for relapse used to model this transition.

Patients who do not re-achieve an adequate response (i.e., F-VASI90) following retreatment also cease treatment and receive BSC. Therefore, they are modelled as transitioning to the non-response state (where they receive BSC) and remain in this state for the duration of the modelled time horizon or until death, whichever occurs first. This transition is modelled using data from patients in Cohort B from the TRuE-V LTE study. Data from patients who did not achieve an F-VASI75 response at week 52 in the TRuE-V studies and were re-randomised to ruxolitinib cream in the TRuE-V LTE study but did not subsequently achieve F-VASI90 at week 104 (4) inform this transition.

After transitioning to the non-response state from either the initial period, maintenance period or stable states (including retreatment), patients receive BSC (modelled as residence in the non-response state) for ten years. The length of time patients receive BSC is explored in scenario analysis.

Patients can transition to the ‘dead’ absorbing state from all health states at any time point due to all-cause mortality as per general UK population mortality; details are provided in Section B.3.3.6*Mortality*

B.3.2.3 Features of the economic analysis

Key features implemented in the economic analysis and their justifications are presented in **Table 30** below.

The model implements 4-week cycles that are half-cycle corrected. This cycle length reflects the time points of response assessment in the pooled TRuE-V1 and TRuE-V2 trials (2, 3) and is aligned with cycle lengths used in other dermatological conditions, such as atopic dermatitis (117, 118). Where necessary, model input variables were rescaled to the relevant cycle length duration (e.g., sustained response, relapse, regain response, no regain response, no response, annual mortality rates, discontinuation).

Given that vitiligo is a chronic disease, a lifetime horizon of 63 years was deemed appropriate, applied based on the mean age (37.8 years) of the prior therapy sub-group from the pooled TRuE-V trial population; shorter time horizons were explored in scenario analyses. Patients are all assumed to die at 100 years since Office for National Statistics (ONS) life tables for mortality end at 100 years (124).

Costs considered in the model include drug acquisition costs, disease management costs, administration costs and adverse event costs.

Utility values included in the model base case are based on a mapping algorithm, which enabled the prediction of EQ-5D-3L utilities using the Alava crosswalk from F-VASI and VNS data collected in the TRuE-V studies (125).

Costs and effects are discounted annually at 3.5%, as per the NICE reference case (116).

The incremental cost-effectiveness ratio (ICER) of ruxolitinib cream versus vehicle cream is evaluated in terms of the incremental cost per QALY gained.

Table 30. Features of the economic analysis

Factor	Chosen values	Justification
Model structure	Markov state-transition model with 7 health-states	The model structure was conceptualised to reflect the natural history of vitiligo as well as the disease-specific care pathway for vitiligo in England. On this basis, a Markov state-transition model approach was chosen, with health states defined to capture the journey of vitiligo patients through the care pathway. The structure has been validated with clinicians and health economists (121, 122).
Cycle length	4-weekly cycles	The 4-weekly cycle length reflects the time points of response assessment in the clinical trials and is aligned with cycle lengths used in other dermatological conditions, such as atopic dermatitis (93, 117).
Time horizon	Lifetime	In line with the NICE reference case and reflective of the chronic nature of vitiligo (116)
Treatment waning effect	No treatment waning assumed	Loss of treatment response in patients with vitiligo is clinically measurable and will therefore lead to treatment discontinuation. As such, discontinuation is a suitable proxy for treatment waning (93)
Perspective of the analysis	NHS and PSS	In line with the NICE reference case (116)
Discounting	3.5%	In line with the NICE reference case (116)
Source of utilities	EQ-5D-3L mapped from F-VASI and VNS	Utilities are mapped from vitiligo-specific measures due to the unsuitability of broader dermatological measures for vitiligo and the paucity of existing relevant mapping algorithms. Mapping from repigmentation scores (RPS) using polynomial models appeared to perform best followed by VNS, producing the least difference between mean observed and predicted utilities, lowest Akaike Information Criterion (AIC) and mean absolute error (MAE) values in statistical testing (126). RPS is an appropriate proxy for F-VASI as described in section **Error! Reference source not found.**

		Furthermore, F-VASI response was the primary endpoint, and VNS was the secondary endpoint in the TRuE-V studies (93). As such, utility mapping from these endpoints were used for the base case and scenario analyses, respectively.
Source of costs	NHS Reference Costs 2021/22 (127), Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care 2021 (128), British National Formulary online (129), Sach et al. 2021 (112), clincial expert opinion	Established sources of costs within the NHS; in line with NICE reference case (116), where cost data were not available, the published literature and clinical experts were consulted.
Resource use	Based on Sach et al. (2021) (112) and adapted to reflect cost categories based on TA681 (118). BSC (received by patients in the non-response state) and concomitant therapy proportions sourced from the VALIANT study (vitamin D proportion is based on clinical expert opinion) (122, 130).	Resource use categories reported by Sach et al. (2021) (112) – which was identified as part of the economic systematic review – were slightly modified to align with previous NICE submissions in other dermatological conditions (118). The updated categories were validated with clinical experts in vitiligo (122). Full details are presented in Appendix M. VALIANT is a cross-sectional study of vitiligo, considered to be reflective of clinical practice. The study collected survey data on patient usage and HCP-recommended treatments for vitiligo. A simple average of treatment strategies reported by patients and recommended by HCPs is taken, as the resultant proportions were most closely aligned with clinical expert feedback on treatment proportions in practice (122, 130).
Health effects measure	QALYs	In line with the NICE reference case (116)
Half-cycle correction applied	Yes	Half-cycle correction is applied in the model to account for events and transitions occurring at any point in the cycle

Abbreviations: BNF, British National Formulary; BSC, best supportive care; CEA, cost effectiveness analysis; EQ-5D-5L, EuroQol-5 Dimension-5 Level; F-VASI, facial vitiligo area scoring index score; HCP, health care practitioner; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, Personal and Social Services; PSSRU, Personal Social Services Research Unit; RPS, Repigmentation score; RWE, real world evidence; QALYs, quality adjusted life years; VALIANT, vitiligo and Life Impact Among International Communities; VNS, vitiligo noticeability scale.

B.3.2.4 Intervention technology and comparators

The intervention of interest is ruxolitinib cream for topical application to depigmented skin areas, in line with the TRuE-V trials (93), the marketing authorisation (19) and the decision problem.

There is no published NICE guidance for the treatment of vitiligo in England as no licensed treatments existed before ruxolitinib cream.

The BAD guidelines for the management of people with vitiligo recommend first line treatment with TCS or TCI, and second line treatment with phototherapy +/- TCS or TCIs (7). The widespread availability of generic TCS and TCIs in UK clinical practice has led to common usage as a first-line therapeutic option (131). Despite being recommended in clinical guidelines, phototherapy usage for vitiligo in clinical practice in England is limited by its varying availability within the NHS and stretched resources leading to extensive waiting lists when this is accessible. These inconsistencies reflect an unmet need for access to phototherapy for patients suffering with vitiligo in England. Further, phototherapy can be demanding for patients with three-weekly appointments for nine months, placing a large burden on patients (7).

Ruxolitinib cream is proposed to be positioned as a step change option between the first and second line for adults and adolescents with NSV with facial involvement from 12 years of age 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. Therefore TCS, TCI and phototherapy are not relevant comparators.

Notwithstanding, comparisons with off-label treatments used for the management of vitiligo were explored in an ITC FA. Considerable quality issues were detected including medium to high risk of bias in the majority of studies, heterogeneity in study designs, small sample sizes, lack of mutually defined or reported endpoints, substantial imbalances in population characteristics, as well as sparse and mostly disconnected evidence networks. As a result, robust evidence synthesis for generation of treatment effect estimates for ruxolitinib cream relative to TCS, TCI or phototherapy was not feasible. Therefore, the comparator in the cost-effectiveness analysis is vehicle cream, as captured in the TRuE-V studies.

B.3.3 Clinical parameters and variables

B.3.3.1 Overview of efficacy data and approach to data analysis

As described in Section B.3.2.2 Model structure, the model consists of seven mutually exclusive health states. The efficacy data informing the cost-effectiveness analysis are based on the pooled TRuE-V studies (94) and the TRuE-V LTE study (4). **Table 31** presents the data used in the model, while the subsequent section describes how these data are used to inform the model. Data used in the model are derived from the pooled data and/or the LTE, with the calculations performed presented in Appendix M.

As described in Section B.3.3.3 Clinical efficacy inputs and Section B.2 Clinical effectiveness, efficacy data for vehicle cream are not available beyond 24 weeks from the TRuE-V studies. Therefore, efficacy inputs for vehicle cream beyond week 24 are based on assumptions described in the subsequent sections (Section B.3.6.2).

Table 31. Summary of data used to inform the cost-effectiveness analysis

Model Transition	Description	Section	Data Source
Initial Response	Derived from the proportion of patients in each respective arm achieving a response of F-VASI75 at 24 weeks, the primary endpoint of the trial.	Section B.3.3.3.1 Treatment initial response probabilities at 24 weeks	Pooled TRuE-V1 and TRuE-V2 data (Phase III) (94)
Sustained Response	Proportion of patients who achieve F-VASI90 at week 52, conditional on having achieved F-VASI75 at 24 weeks, i.e., the initial period. Due to lack of comparative data beyond 24 weeks, an OR was applied to estimate vehicle cream data; a conservative assumption of equal treatment effects is assumed between intervention and comparator after week 24.	Section B.3.3.3.2 Treatment sustained response probabilities at 52 weeks	
Relapse	Derived from 'Time to F-VASI<75' data from the vehicle cream arm of Cohort A in the TRuE-V LTE study. Vehicle cream data are used in the base case as it is assumed that patients are not treated in the stable state. ORs are used to derive ruxolitinib cream arm with a conservative assumption of equal treatment effect (i.e., an OR of 1.0 is applied)	Section B.3.3.3.3 Treatment relapse probabilitiesB.3.3.3.3 Treatment relapse probabilities	TRuE-V LTE (Phase III) (4)
Regain Response	Derived from 'Time to regain response' data defined by F-VASI90 from the vehicle cream arm of Cohort A in the TRuE-V LTE study that have relapsed and retreated with ruxolitinib cream. Vehicle cream data are used in the base case as patients would be off treatment in the health state they reside in prior to transitioning; ORs are used to derive ruxolitinib cream arm with a conservative assumption of equal treatment effect (i.e., an OR of 1.0 is applied)	Section B.3.3.3.4 Retreatment B.3.3.3.4 Retreatment	TRuE-V LTE (Phase III) (4)

No Regain Response	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. Ruxolitinib cream data are used in the base case as patients in Cohort B of the TRuE-V LTE study were re-randomised to ruxolitinib cream and study design constraints meant that data from Cohort A could not be used. ORs are used to derive vehicle cream arm with a conservative assumption of equal treatment effect (i.e., an OR of 1.0 is applied).	Section B.3.3.3.4 Retreatment	
No Response	In the absence of relapse data for previously re-treated patients that 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	Section B.3.3.3.4 Retreatment	
Discontinuation	Based on treatment discontinuation data from the pooled TRuE-V studies	Section B.3.3.4 *Discontinuation*	Pooled TRuE-V1 and TRuE-V2 data (Phase III) (94)

Abbreviations: F-VASI, facial vitiligo area scoring index; F-VASI75, 75% to 89% improvement from baseline in F-VASI; F-VASI90, 90% or greater improvement from baseline in F-VASI; OR, odds ratio.

B.3.3.2 Baseline Patient Characteristics

Given the anticipated positioning of ruxolitinib cream as a step change option between first and second line treatment, the 'prior therapy' subgroup was selected for the base case analysis, based on pooled TRuE-V1 and TRuE-V2 data (94). Baseline characteristics for the prior therapy subgroup, the overall population and the Fitzpatrick skin type IV-VI subgroup are presented in **Table 32** below. The characteristics of the prior therapy subgroup and the overall population are broadly similar. The overall population and Fitzpatrick skin type IV-VI subgroup are utilised in scenario analyses. No differences in population characteristics are assumed between ruxolitinib and vehicle cream. Subgroup data (i.e., prior therapy and Fitzpatrick IV-VI) is not available for the retreatment data inputs; the inputs used to define these transitions are based on the overall population. The Fitzpatrick IV-VI categorisation was chosen as darker skin types are associated with a greater patient burden (18) including the use of a significantly greater number of vitiligo treatments (132). This categorisation has been used in a recent study which found that facial involvement is reflective of patients' global perception of vitiligo extent (56).

Table 32. Baseline characteristics of populations considered in the analyses

Characteristic	Prior therapy (N=411)		Overall (N=674)		Fitzpatrick skin type IV-VI subgroup (N=188)	
	Mean value	SE	Mean value	SE	Mean value	SE
Age (years)	37.8	0.76	39.6	0.58	39.7	1.04
Weight (kg)	74.7	0.86	77.5	0.70	80.3	1.36
Female (%)	55.7	0.03	53.1	0.02	47.3	0.04

Abbreviations: SE, standard error.
Source: Incyte. Baseline characteristics of populations considered in the cost-effectiveness analyses [Data on file] (133).

B.3.3.3 Clinical efficacy inputs

The sections below describe the clinical inputs used in the cost-effectiveness analysis in the base case. **Table 33** presents the clinical data used in the model. Data inputs used for the overall population and the Fitzpatrick skin type IV-VI subgroup are provided in Appendix M.

Table 33. Clinical data applied in model in the base case

Response category	Ruxolitinib cream		Vehicle cream		Section	Source
	Efficacy	SE	Efficacy	SE		
Initial and sustained response						
Initial response (F-VASI75 at week 24)*	[redacted]	[redacted]	[redacted]	[redacted]	Section B.3.3.3.1 Treatment initial response probabilities at 24 weeks	Derived from pooled results of TRuE-V1 and TRuE-V2 data (Phase III) (94)
Sustained response F-VASI90 at week 52	[redacted]	[redacted]	Equal treatment effect assumed		Section B.3.3.3.2 Treatment sustained response probabilities at 52 weeks	
Relapse						
Time to relapse data (i.e., time to F-VASI<75) at week 104	Equal treatment effect assumed		[redacted]	[redacted]	Section B.3.3.3.3 Treatment relapse probabilities	Derived from Cohort A TRuE-V LTE (Phase III) (4)
Retreatment						

Regain response (F-VASI90 at week 104)	Equal treatment effect assumed		[redacted]	[redacted]	Section B.3.3.3.4 Retreatment	Derived from Cohort A TRuE-V LTE (Phase III) (4)
No regain response (F-VASI<75 at week 52 and F-VASI<90 at week 104)	[redacted]	[redacted]	Equal treatment effect assumed		Section B.3.3.3.4 Retreatment	Derived from Cohort B TRuE-V LTE (Phase III) (4)
Loss of response following retreatment (stable retreated)	Equal treatment effect assumed[redacted]	[redacted]	Equal treatment effect assumed		Section B.3.3.3.4 Retreatment	Derived from Cohort A TRuE-V LTE (Phase III) (4)
Discontinuation						
Initial period	[redacted]	[redacted]	[redacted]	[redacted]	Section B.3.3.4 *Discontinuation*	Derived from pooled results of TRuE-V1 and TRuE-V2 data (Phase III) (94)
Maintenance period	[redacted]	[redacted]	[redacted]	[redacted]	Section B.3.3.4 *Discontinuation*	

Notes: *Initial response is broken down into mutually exclusive FVASI75-89 and FVASI90 categories for modelling purposes. ** No regain response was calculated using the simple average of two approaches to missing data (removing missing data and treating missing data as non-responders). Data presented in this table has been derived from pooled results of the TRuE-V studies and/or TRuE-V LTE. These data are presented in Appendix M.
Abbreviations: F-VASI, facial vitiligo area scoring index; F-VASI75, 75% or greater improvement from baseline in F-VASI; F-VASI90, 90% or greater improvement from baseline in F-VASI; NR, Not reported; SE, standard error.

B.3.3.3.1 Treatment initial response probabilities at 24 weeks

The proportion of patients achieving an initial response is used to define the transition from the initial period to the maintenance period. Initial response is defined as the proportion of patients achieving F-VASI75 (i.e., ≥75% improvement from baseline in the face vitiligo area scoring index), as clinically validated and aligning with the primary endpoint of the TRuE-V trials (93). **Table 33Error! Reference source not found.** presents the probabilities of achieving initial response of F-VASI75 at week 24 for ruxolitinib cream and vehicle cream; [redacted] (estimated as [redacted] achieving an F-VASI score of 75-89 and [redacted] achieving F-VASI90, given that the response categories in the model are not inclusive) and [redacted] (estimated as [redacted] achieving an F-VASI score of 75-89 and [redacted] achieving F-VASI90, given that the response categories in the model are not inclusive) of patients treated with ruxolitinib cream and vehicle cream, respectively, achieved F-VASI75 (2, 3). At week 24, these respective proportions of the modelled cohort transition to the 'maintenance' health state in their respective arms.

B.3.3.3.2 Treatment sustained response probabilities at 52 weeks

The proportion of patients achieving a sustained response defines the transition from the maintenance to the stable health state.

The efficacy data for ruxolitinib cream was obtained from the TRuE-V clinical trials, wherein patients who achieved an initial response level of F-VASI75 after 24 weeks continued ruxolitinib cream until the end of the open-label extension period at 52 weeks. Patients who achieved F-VASI75 at week 24 *and* F-VASI90 at week 52 were considered to have achieved a sustained response. F-VASI90 was selected for the sustained response definition at 52 weeks to align with the eligibility criteria of Cohort A of the TRuE-V LTE study (4), in which patients were required to have achieved F-VASI90 to be enrolled. The use of F-VASI90 rather than a less stringent F-VASI response level (e.g., F-VASI75) to define a sustained response is a conservative assumption that has been validated by clinical experts (122).

The proportions of patients achieving a sustained response are listed in **Table 33Error! Reference source not found.**. These patients transition to the stable health state at the 52-week response assessment and on a cycle-by-cycle basis thereafter. Patients who do not achieve a sustained response, indicated by an initial response of F-VASI75 followed by F-VASI<90 in the sustained response assessment, remain in

the maintenance state until treatment discontinuation due to any cause, see Section B.3.3.4 *Discontinuation* for discontinuation rates.

Efficacy data for vehicle cream are unavailable beyond week 24; therefore, assumptions were necessary to determine the sustained response for patients in the vehicle cream arm in the sustained response assessment at week 52. An OR was used to estimate the relative effect of a sustained response for vehicle cream compared to ruxolitinib cream. A conservative assumption of 1.0 was selected and validated by a health economic expert (121), implying equal sustained response rates between treatment arms from week 24 to week 52 (See **Table 33Error! Reference source not found.**).

B.3.3.3.3 Treatment relapse probabilities

The transition from stable to the re-treated health state is informed by time-to-relapse data (i.e., time to F-VASI<75) from the vehicle cream arm of Cohort A in the TRuE-V LTE study (4). Patients in Cohort A were randomised to either ruxolitinib cream or vehicle cream and followed up between week 52 and week 104. As patients within the stable state are not receiving treatment, relapse data from the vehicle arm of Cohort A is the most appropriate for modelling relapse.

In order to calculate the probability of relapse, as presented in **Table 33Error! Reference source not found.** rates were calculated from patient-level data of the TRuE-V LTE study (4). The total number of relapse events was divided by the total sum of patient observation time across the available follow-up period. [redacted] relapse events were observed in 56 patients, with their individual available observation time summing to [redacted] days. This gave [redacted] events per day. In order to be able to inform the transition in the Markov model, the rate was converted using the standard formula below under the assumption of a constant hazard:

(1–EXP (LN (1-[redacted])/(1/28))

This provided a per cycle relapse probability of [redacted] applied to the stable health state in the vehicle cream arm, which was validated with the clinical experts (122).

B.3.3.3.4 Retreatment

In line with clinician feedback, patients who had previously responded to treatment but had since stopped receiving treatment and had experienced a relapse would be

retreated (122). The model explicitly considers this with the inclusion of ‘retreated’ and ‘stable retreated’ health states. All patients who relapse are modelled as transitioning to the retreated health state, where they are retreated with either ruxolitinib cream or vehicle cream. Following retreatment, patients transition to either the stable retreated health state or the non-response health state based on whether a response is regained. That is, patients who regain a response transition to the retreated stable health state and those who do not regain a response transition to the non-response health state where they receive subsequent BSC.

The transition to the stable retreated health state is based on the time to regain an F-VASI90 response for patients on vehicle cream in Cohort A of the TRuE-V LTE study (4). This definition of response was used as it aligns with the definition of a sustained response (which allows the transition from the maintenance period health state to the stable health state). Transitions are defined by the per-cycle rate of regaining F-VASI90 response and calculated using the same formula as for relapse (Section B.3.3.3.3 Treatment relapse probabilities) under a conservative assumption of constant hazard. Specifically, 11 patients in the TRuE-V LTE study regained F-VASI90 out of 16 patients who had been retreated, with their individual observation time summing to [redacted] days. This translates into [redacted] regain of response events per day. Utilising the constant hazard approach as detailed in Section B.3.3.3.3 Treatment relapse probabilities above, this yields a probability of regaining a response of [redacted] per cycle, applied to the retreated health state in the vehicle cream arm. Vehicle cream data was chosen for this transition as patients had been in the stable state, where no treatment was being received. A conservative assumption of equal efficacy for ruxolitinib cream versus vehicle cream was applied with the OR of regaining response set to 1.

If patients subsequently lose their regained response in the stable retreated state (defined as an F-VASI<75 in line with the definition of relapse), patients then transition to receive BSC in the non-response state. The transition from stable retreated to non-response is modelled using the same assumptions as relapse (Section B.3.3.3.3 Treatment relapse probabilities), with a [redacted] per cycle relapse probability applied to the stable retreated health state in the vehicle cream arm with equal treatment effects assumed for ruxolitinib cream.

The transition probabilities for those patients not regaining a response in the retreated state are informed by week 104 shift summary response data from Cohort B of the TRuE-V LTE study (**Table 34**) (4). This analysis uses data from patients who achieved F-VASI<75 (including F-VASI50-<75, F-VASI25-<50, <F-VASI25) at week 52 and F-VASI<90 (including F-VASI75-<90, F-VASI50-<75, F-VASI25-<50, <F-VASI25) at week 104 (n=58). However, data for 24 patients who achieved F-VASI<75 at week 52 were missing at the week 104 response assessment. Two methods to account for these missing data were used in the analysis: firstly, removing missing data from the overall sample of those with F-VASI<75 at week 52 (n=99) and secondly, treating missing data as non-responders.

For the first method, the probability of having F-VASI<90 at week 104 if patients with F-VASI<75 at week 52 is calculated as [redacted] ([redacted]); for the second method the probability is [redacted] ([redacted]). In the base case, a simple average of the two methods is applied, giving an overall probability of [redacted] This probability was converted to a per cycle response probability for no regain of response using the same formula as mentioned in Section B.3.3.3.3 Treatment relapse probabilities, giving [redacted] per 4-week cycle applied to the re-treated health state. Data for patients re-randomised to ruxolitinib cream within Cohort B of the TRuE-V LTE study was used as, due to study design constraints, data collected in Cohort A could not inform this transition. An OR assuming equal treatment effects (i.e., 1.0) is applied for vehicle cream, as a conservative assumption.

Table 34. Shift summary of F-VASI from Week 52 to Week 104. Cohort B, TRuE-V LTE (4)

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-VASI25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F-VASI 25-<50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F-VASI 50-<75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F-VASI 75-<90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F-VASI90	[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 (4)

B.3.3.4 *Discontinuation*

Discontinuation rates can be found in **Table 33Error! Reference source not found.** above. Patients can discontinue treatment due to all causes in the intervention or comparator arms in the initial period (excluding lack of efficacy) and maintenance period. The discontinuation refers to all discontinuation reasons, including lack of efficacy, rapid cessation of symptoms, adverse events, physician or patient decision, and any other reason that led to dissatisfaction and discontinuation of the medication. Treatment-specific discontinuation rates were derived from the pooled data of the TRuE-V studies (94) 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 24. In contrast, discontinuation rates during the maintenance period relate to all causes, including lack of efficacy, as informed by data from week 24 to week 52.

In the TRuE-V trials, participants initially receiving vehicle cream transitioned to ruxolitinib cream at the 24-week mark (93). Consequently, the discontinuation rate of vehicle cream during the maintenance phase was determined based on the number of patients who received vehicle cream up to week 24, switched to ruxolitinib cream at week 24 and subsequently discontinued ruxolitinib cream between weeks 24 and 52.

No discontinuation is assumed in the 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.

B.3.3.5 *Adverse events*

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) (134). The model includes TEAEs that occurred in ≥4% of patients in any group in the 24-week period. The rates of included adverse events are based on data from the safety population during the double-blind phase of the pooled TRuE-V studies and are reported in **Table 35** (134). The AEs were not modelled as separate health

states, instead the rates and the consequences of AEs were included in the costs accumulated in each model cycle. Since the AEs reported in the TRuE-V1 and TruE-V2 trials were mild and a significant impact on HRQoL is not expected, disutility due to AEs is not included in the base case analysis. This is in line with previous NICE submissions in dermatology (117, 118).

Table 35. Rates of adverse events

Adverse event	Ruxolitinib cream (N=449)		Vehicle cream (N=224)		Source
	Rate	SE	Rate	SE	
Application site acne	6.24%	0.011	1.34%	0.008	Derived from all-grade AE rates from the pooled TRuE-V trials (134). Converted from 24-week rates to 4-week probabilities
Application site pruritus	6.46%	0.012	3.57%	0.012	
Nasopharyngitis	4.45%	0.010	2.23%	0.010	
Headache	5.57%	0.011	2.68%	0.011	
Upper respiratory tract infection	3.34%	0.008	2.23%	0.010	

*Adverse events were derived from pooled TRuE-V data and calculated as incidence rates
Abbreviations: SE, standard error
Source: Incyte. Cost effectiveness model technical report [Data on file] (134).

B.3.3.6 *Mortality*

Patients are at risk of general population mortality at every timepoint in the model, irrespective of the treatment. Patients with vitiligo are assumed to have the same mortality rate as the general population given that vitiligo has no direct impact on mortality (135). Age-specific mortality rates were derived from the latest ONS national UK life tables for 2018-2020 (124) weighted by the male-female ratio observed in the TRuE-V trials (93) (**Table 32**).

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life studies

Details on the SLR conducted to identify the published evidence on HRQoL studies are presented in Appendix H. Twenty-four interventional studies investigated the impact of vitiligo on HRQoL. No mapping algorithms in vitiligo were identified; a number of such mapping algorithms are available in psoriasis and atopic dermatitis (136-139). Through collaboration with an external academic group, Incyte has since become aware of mapping algorithms in vitiligo using data from a UK NIHR-sponsored pragmatic RCT (HI-Light trial) (125).

B.3.4.2 Health-related quality-of-life data from clinical trials

EQ-5D data were not collected in the TRuE-V1 and TRuE-V2 trials. The mapping algorithms developed by Begum et al. (2023) were applied to the TRuE-V outcomes (F-VASI and VNS) to generate utilities for the cost-effectiveness analysis (125).

B.3.4.3 EQ-5D utility mapping

Begum et al. (2023) provide mapping algorithms to generate EQ-5D mapped utilities for RPS, VNS and VitiQoL, respectively (125). Begum et al. (2023) reported that mapping from RPS using polynomial models appeared to perform best, followed by VNS, producing the least difference between mean observed and predicted utilities, lowest Akaike Information Criterion (AIC) and mean absolute error (MAE) values in statistical testing (125).

RPS is considered an appropriate proxy for F-VASI given the notable similarities between how RPS and F-VASI are measured. A standard approach was used to measure total affected area; the sum of lesions was expressed as a fraction of the total BSA. The resulting CFB in total BSA informs RPS categorisation. The categorisation of repigmentation for RPS in HI-Light is consistent with that of F-VASI in the TRuE-V studies. In the HI-Light trial, repigmentation was classified in an identical manner to the TRuE-V trials: (0%–24%, 25%–49%, 50%–74%, and 75%–100%). Although the measurement of RPS included lesions from the ‘head and neck’, ‘hands and feet’ or ‘rest of the body’, a covariate accounting for lesion location (face versus hands/feet) was initially incorporated into the polynomial regression model. However, Begum et al, 2023 (125) reported the subsequential elimination of this covariate during

the refinement process because it was not considered to be a statistically important predictor of utility ($p > 0.05$). Moreover, the authors demonstrated that the RPS provided a more robust mapping algorithm based on key performance metrics and using criteria and methods provided in TSD 22 (140). As such, the RPS is considered an appropriate proxy for F-VASI.

The polynomial algorithm used to predict EQ-5D utilities from F-VASI is reported in Begum et al. (2023) as (125):

$$EQ\text{-}5D_{F\text{-}VASI} = 0.709 + (0.0119 * \text{F-VASI Category}) - (0.000214 * \text{F-VASI Category}^2) + (0.00000118 * \text{F-VASI Category}^3)$$

The polynomial algorithm used to predict EQ-5D utilities from VNS is reported in Begum et al. (2023) as (125):

$$EQ\text{-}5D_{VNS} = 1.1656 - (0.465 * \text{VNS Score}) + (0.262 * \text{VNS Score}^2) - (0.0599 * \text{VNS Score}^3) + (0.00481 * \text{VNS Score}^4)$$

Algorithms to predict EQ-5D utilities from VitiQoL are also presented in Begum et al. (2023) (125). Baseline values could not be obtained through F-VASI or VNS metrics, as these measures represent changes from the baseline, and the TRuE-V studies did not collect baseline data (90, 91). As a result, baseline estimates were derived by mapping total VitiQoL score (Question 1 – Question 16) from the TRuE-V studies to EQ-5D utility scores using the Bayesian linear algorithm found in Begum et al. (2023) (125). The justifications for the approach are presented in the technical report provided in Appendix O, which also further describes the appropriateness of HI-Light derived mapping algorithms' application to the TRuE-V trial data.

B.3.4.3.1 Application of mapping algorithms to TRuE-V

The mapping algorithms reported by Begum et al. (2023) (125) were used to estimate EQ-5D utilities at week 24 based on F-VASI and VNS outcome data, respectively, collected in the TRuE-V studies (90, 91, 94). Utilities were estimated using a change from baseline methodology, specifically, the change from baseline at week 24.

Before the mapping algorithms could be applied, F-VASI percentage change from baseline scores to week 24 from pooled TRuE-V data were grouped into categories and appropriate adjustments were made to reflect repigmentation versus depigmentation as per recommendations in Begum et al. (2023) (125). Where F-VASI percentage change from baseline implied depigmentation of skin (i.e., worsening),

patients were classified into 2 possible 'depigmentation categories' after examining the average mean F-VASI change from baseline in those with skin depigmentation at week 24. For utilities from F-VASI using data from TRuE-V studies, scores for patients with depigmentation were truncated to those having skin pigmentation loss ≤37.5% (category –37.5% to –1%), as this was considered more conservative (i.e., even if patients had greater de-pigmentation than 37.5%, mainly on the placebo, the loss of skin colour was restricted to 37.5% as a more conservative approach). Mean depigmentation for patients across both arms was 37.68%, which provides some justification for the proposed categorisation. Two further categories (–25% to –1%; –50% to –1%) for sensitivity analyses were included.

Table 36 below presents the banding levels and a description utilised in the mapping.

Table 36. F-VASI bandings utilised in the mapping algorithms

Name	Banding	Description
F-VASI (DP: -25%)	Depigmentation categorisation I: Percentage change of -25% The value of 25% is set as a suitably conservative amount of skin pigmentation loss, based on the mean skin pigmentation loss experienced for patients on ruxolitinib cream (mean depigmentation of 25.34%).	All patients with depigmentation were truncated to having skin pigmentation loss not greater than 25%
F-VASI (DP: -37.5%)	Depigmentation categorisation II: Percentage change of -37.5% The value of 37.5% is based on the combined mean skin pigmentation loss experienced for patients across both arms	All patients with depigmentation were truncated to having skin pigmentation loss not greater than 37.5%
F-VASI (DP: -50%)	Depigmentation categorisation III: Percentage change of -50%	All patients with depigmentation were truncated to having skin pigmentation loss not greater than 50%

Abbreviations: DP, depigmentation; F-VASI, facial vitiligo area scoring index
Source: Incyte, technical report for statistical analysis and utility modelling [Data on file] (126)

F-VASI (DP: -37.5%) was chosen for the base case analysis as the repigmentation response was considered the most aligned with clinical practice and mean depigmentation (%) was consistent with that observed in the TRuE-V studies. F-VASI (DP: -25%) is explored in scenario analyses, whereas F-VASI (DP: -50%) based estimates were not explored in the model due to providing estimates outside of the

range of values suggested in the latest NICE technical support document for utilities (126, 140).

B.3.4.4 Health-related quality-of-life data used in the cost-effectiveness analysis

Table 37 presents the utility values used in the base case cost-effectiveness analysis, whereas **Table 38** presents alternative utility values explored in scenario analyses, both sets of utility values reported are calculated using prior therapy subgroup data.

Table 37. Summary of utility values for cost-effectiveness analysis base case

State	Utility value: mean (standard error)	95% CI (Lower: Upper)	Reference in submission (section and page number)	Justification
Baseline	0.879 (0.003)	0.874, 0.884	**Error! Reference source not found.**	VitiQoL baseline utilised as F-VASI mapping produced no available baseline data (126)
No response	-0.082*	-0.087, -0.077	**Error! Reference source not found.**	F-VASI (DP: -37.5%) was the best performing measure in the mapping algorithm (126)
F-VASI50-74	0.010*	-0.007, 0.028	**Error! Reference source not found.**	
F-VASI75-89	0.056*	0.037, 0.074	**Error! Reference source not found.**	
F-VASI90	0.066*	0.047, 0.084	**Error! Reference source not found.**	

Abbreviations: F-VASI, facial vitiligo area scoring index; 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; VitiQoL, vitiligo-specific quality-of-life instrument
Source: Incyte, technical report for statistical analysis and utility modelling [Data on file] (126)

Table 38. Summary of utility values for scenario analyses

Mapping	State	Utility value: mean (standard error)	95% CI (Lower: Upper)	Reference in submission (section and page number)	Justification
F-VASI (DP: -25%)	Baseline	0.879 (0.003)	0.874, 0.884	**Error! Reference source not found.**	VitiQoL baseline utilised as F-VASI mapping produced no available baseline data (126)
	No response	-0.046	-0.052, -0.040	**Error! Reference source not found.**	F-VASI (DP: -25%) produces a clinically plausible

	F-VASI50-74	0.010	-0.005, 0.025	**Error! Reference source not found.**	repigmentation response (126)
	F-VASI75-89	0.056	0.040, 0.072	**Error! Reference source not found.**	
	F-VASI90	0.066	0.050, 0.081	**Error! Reference source not found.**	
VNS	Baseline	0.879 (0.003)	0.874, 0.884	**Error! Reference source not found.**	VitiQoL baseline utilised as F-VASI mapping produced no available baseline data (126)
	No response	0.014	0.007, 0.021	**Error! Reference source not found.**	VNS was the secondary endpoint in the TRuE-V studies (93).
	F-VASI50-74	0.012	-0.001, 0.024	**Error! Reference source not found.**	
	F-VASI75-89	0.014	-0.001, 0.029	**Error! Reference source not found.**	
	F-VASI90	0.025	0.011, 0.040	**Error! Reference source not found.**	

Abbreviations: F-VASI, facial vitiligo area scoring index; 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; VitiQoL, vitiligo-specific quality-of-life instrument
Source: Incyte, technical report for statistical analysis and utility modelling [Data on file] (126)

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

Please refer to Section B.3.1 Published cost-effectiveness studies for details on the economic SLR which also identified HCRU studies. In total, eleven publications were identified with cost and healthcare resource use data for patients with vitiligo. Details on the methods and results are presented in Appendix I.

The following cost categories are included in the model base case: drug acquisition costs (Section B.3.5.1 Drug Acquisition Costs), disease management (Section B.3.5.2 Disease Management Resource Use and Costs) and AEs (Section

B.3.5.3 Adverse). All costs are based on routine NHS sources including NHS reference costs (127), PSSRU (141) and the British National Formulary (BNF) (129). Costs were inflated using the ONS CPIH index where necessary (142). Patients receiving the intervention and comparator both receive concomitant therapies, assumed equally available in both arms. No treatment administration costs are assumed for any treatment included in the model.

B.3.5.1 Drug Acquisition Costs

Intervention and Comparator

Treatment acquisition costs for ruxolitinib cream and vehicle cream are presented in **Table 39**. Ruxolitinib cream is a twice-daily treatment applied topically to the depigmented skin areas up to a maximum of 10% of BSA. The model assumes a daily dose based on the observed median weight of intervention and vehicle cream (4.03g) applied during the 24-week period in the pooled TRuE-V studies (2, 3, 94) and converted to use per cycle. Clinicians described that compliance in clinical practice is expected to be lower than that of the trials (122), meaning that costs modelled for ruxolitinib cream in the cost-effectiveness model reflect a conservative estimation. For vehicle cream, one gram is assumed equivalent to one millilitre. The dose frequency is based on the TRuE-V studies and is in line with the MHRA license (2, 3). The cost of vehicle cream is assumed equivalent to that of Uvistat Sun Cream SPF 50 (125 mL) (inflated to cost year 2022), an Advisory Committee on Borderline Substance approved sunscreen (143), in line with clinical validation (122).

Concomitant Therapy

Patients receiving ruxolitinib cream and vehicle cream are assumed to use concomitant therapies which include vitamin D supplements, camouflage, fixing powder and sunscreen following suggestion from clinical experts. The amount used for these therapies was not collected in the TRuE-V studies (2, 3, 94); daily doses were based on the simple average of inputs provided by clinical experts. The proportion of patients receiving such therapies is assumed to be the same as the respective therapies used in BSC.

Unit costs for vitamin D supplement, camouflage and fixing powder were sourced from the BNF (129), with sunscreen sourced from the NHS East and North Hertfordshire

Clinical Commissioning Group (CCG) (143) and inflated to cost year 2022 using the ONS CPIH index (142).

Intervention/comparator and concomitant therapy costs are applied in the initial period, maintenance period and re-treatment states, whereas patients in the stable health states do not incur any intervention/comparator or concomitant therapy costs.

Best Supportive Care

Patients in the non-response health state receive BSC, consisting of NB-UVB, vitamin D supplement, camouflage, fixing powder and sunscreen. The proportion of patients on BSC that receive tacrolimus ointment, mometasone ointment and oral dexamethasone is assumed to be 0 based on the positioning of ruxolitinib cream. Similar to concomitant therapies, daily doses were based on the simple average of inputs provided by clinical experts. The proportions of patients on the BSC items are based on UK-specific inputs from the VALIANT study (**Figure 21**), in which a simple average of HCP recommended data and patient use data is used (130), except the vitamin D supplement, for which a 100% proportion was proposed by clinical experts as the proportion sourced from VALIANT appeared low. All proportions sourced from VALIANT (**Figure 21**) (130) were validated with clinicians to ensure they were reflective of UK clinical practice. Unit costs for vitamin D supplement, camouflage and fixing powder were sourced from the BNF (129), with sunscreen sourced from the NHS East and North Hertfordshire Clinical Commissioning Group (CCG) (143) and inflated to cost year 2022 using the ONS CPIH index (142).

For NB-UVB, clinicians stated that patients would undergo three sessions per week for between 9 and 12 months, resulting in a total of 117 and 156 sessions respectively per year, with the former being used in the model as a conservative approach. The model assumes this is repeated on an annual cycle. The cost of £140.84 per session is based on 'Outpatient dermatology procedure tariff (JC47Z)', in line with TA534 (117) and TA681 (118). 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 (144). 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 (144).

Table 40 presents the details on the cost, dosing information and the proportion of patients receiving concomitant therapy and BSC, respectively. BSC costs in the non-response health state are assumed to apply for the first 10 years since the model start following inputs from clinical experts, given that patients would consider discontinuing treatment and visits to the healthcare specialists after a certain period without any improvement. Disease management costs in the non-response health state are assumed to apply for the first 10 years only since the start of model simulation following input from clinical experts who stated that patients would consider discontinuing treatment and visits to the healthcare specialists after a certain period without any improvement (122).

Figure 21. VALIANT Study. Treatment or Management Strategies Ever Used by Patients and Most Frequently Recommended by HCPs, UK Patients (130)

Abbreviations: HCP, healthcare professional; NA, not applicable.
* HCPs frequently recommended medications included those recommended often, very often, or all the time per the questionnaire.
† Medications include vitamins A and D and other.
Source: Incyte, VALIANT (Vitiligo and Life Impact Among International Communities) [Data on file] (130)

Table 39. Costs associated with ruxolitinib cream and vehicle cream

Intervention	Pack cost	Pack size	Dose frequency	Daily dose (Unit)	Cost per Unit	Cost per cycle (4 week)	No. of doses initial period (24 weeks)	No. of doses maintenance period (annual)
Ruxolitinib cream	[redacted]	100g	BID	[redacted]g TRuE-V pooled data* (2, 3, 94)	[redacted]	[redacted]	[redacted]	[redacted]
Vehicle cream	£9.70± BNF (129)	125 mL	BID	[redacted] mL TRuE-V pooled data* (2, 3, 94)	[redacted]	[redacted]	[redacted]	[redacted]

Notes: * TRuE-V pooled median weight of study drug applied daily during 24-week period in total (ruxolitinib cream and BSC) population. ▪ Assumes 365.25 days per year, rounded up. ± BNF price of Uvistat Sun Cream SPF 50 (125 mL) from March 2019, inflated to 2022.
Abbreviations: BID, twice a day; SPF, sun protection factor.

Table 40. Costs associated with concomitant and BSC treatments

Therapy item	Pack size	Pack cost	Daily dose	Sources		Proportion Used	Source
				Pack size & cost	Daily dose		
Concomitant therapy basket							
Vitamin D supplement	48000 IU	£1.99	800 IU	BNF (129)	Clinical expert*	100.00%	Assumed equal to BSC proportion
Camouflage	30.00 g	£11.86	0.74 g	BNF (129)	Clinical expert*	61.70%■	Assumed equal to BSC proportion
Fixing powder	60.00 g	£10.84	0.82 g	BNF (129)	Clinical expert*	61.70%■	Assumed equal to BSC proportion
Sunscreen	500.00 mL	£20.60	4.44 mL	NHS CCG† (143)	Clinical expert*	79.47%■	Assumed equal to BSC proportion

Best Supportive Care basket							
Tacrolimus	60.00 g	£31.64	[redacted] g	BNF (129)	Assumption**; BID	0.00%	Set to 0.00 to reflect the positioning of Ruxolitinib cream
Mometasone	100.00 g	£10.57	[redacted] g	BNF (129)	Assumption**; QD	0.00%	Set to 0.00 to reflect the positioning of Ruxolitinib cream
Vitamin D supplement	48000 IU	£1.99	800 IU	BNF (129)	Clinical expert*	100.00%	Clinical expert input (122)
Camouflage	15.00 g	£11.86	0.62 g	BNF (129)	Clinical expert*	61.70%■	VALIANT study (130, 131)
Fixing powder	60.00 g	£10.84	1.81 g	BNF (129)	Clinical expert*	61.70%■	VALIANT study (130, 131)
Sunscreen	500.00 mL	£20.60	4.44 mL	NHS CCG† (143)	Clinical expert*	79.47%■	VALIANT study (130, 131)
Oral dexamethasone	56.00 mg	£2.81	8.00 mg	BNF (129)	BAD*** (7) BAD*** (7)	0.00%	Set to 0.00 to reflect the positioning of Ruxolitinib cream
NB-UVB	1	£140.84	1	NHS Reference Costs (21/22) (127)	Clinical expert*	[redacted]	VALIANT study (Simple average of HCP recommended and Patient use data) (130)

Notes: † NHS CCG price of sunsense suncream SPF 50 from March 2019, inflated to 2022.
* Simple average of clinical expert inputs
** Single dose of tacrolimus and mometasone assumed equal to ruxolitinib cream.
*** Oral betamethasone 0,1 mg/kg BIW for 3 months. Equivalent dose of alternative oral corticosteroid if oral betamethasone not available.
■Simple average of HCP recommended and patient use data
+ TRuE-V pooled median weight of study drug applied daily during 24-week period in total (ruxolitinib cream and BSC) population.
Abbreviations: BAD, British Association of Dermatologists; BID, twice a day; BIW, twice a week; BNF, British National Formulary; BSC, best supportive care; IU, international unit; QD, Once a day; SPF, sun protection factor.

B.3.5.2 Disease Management Resource Use and Costs

Resource utilisation items and estimates were adapted from Sach et al. (2021) (112) to align with a previous NICE submission in a dermatological indication (TA681) (118), the costing categories presented in Sach et al. (2021) were combined into six costing categories: dermatologist outpatient consultation, dermatologist telephone appointment, dermatologist nurse visit, general practitioner (GP) consultation and accident and emergency (A&E) visit. Clinicians suggested to remove hospitalisations and add psychological support as an additional costing category.

The TCS arm data from Sach et al. (2021) (112) was used to inform resource use in the initial period, maintenance period and re-treated health states, respectively. Resource use for psychological support is based on feedback received during discussions with two dermatologists by taking a simple average of suggested inputs. Resource use in the non-response state follows a similar approach. However, the combination arm (TCS + NB-UVB) data reported by Sach et al. (2021) (112) are used as this reflects second-line positioning for patients who do not respond to TCS. For the stable health states (stable, stable re-treated), dermatologist consultations (outpatient and via telephone) as well as dermatologist nurse visits were based on Sach et al., with the remaining categories based on a simple average approach from suggested values of clinicians. All resource use values are converted from either 9 months (estimates from Sach et al.) or 6 months (estimates obtained from clinicians) to cycle-specific resource use as displayed in **Table 41**. Resource use costs are taken from the latest published sources of NHS reference costs (127) and PSSRU (128); these have been validated with clinicians. Full details of the costing approach is given in Appendix M. Disease management costs in the non-response health state are assumed to apply for the first 10 years only since the start of model simulation following input from clinical experts who stated that patients would consider discontinuing treatment and visits to the healthcare specialists after a certain period without any improvement. This is due to treatment fatigue that patients experience and patient choice varies with time (122).

Table 41. Disease management resource use and costs

Resource use item	Resource use input per cycle	SE	Source	Unit cost	Source
Initial, maintenance periods and retreated					
Dermatologist outpatient consultation	0.411	0.041	Sach et al. (2021) * (TCS arm) (112)	£155.40	NHS Reference Costs ; WAVG of WF01A-D and WF02A-C (127)
Dermatologist telephone appointment	0.002	0.000		£115.44	NHS Reference Costs; WF01C (127)
Dermatologist nurse visit	0.041	0.004		£17.00	PSSRU; per patient contact lasting 15 minutes (128)
GP consultation	0.012	0.001		£42.00	PSSRU; per patient contact lasting 9.22 minutes (128)
A&E visit	0.025	0.003		£220.65	NHS Reference Costs; WAVG of VB06Z-09Z (127)
Psychological support	0.690	0.069	Clinical expert**	£344.21	NHS Reference Costs; weighted average of WF01A–D (127)
Stable disease and stable retreated states					
Dermatologist outpatient consultation	0.192	0.019	Clinical expert**	£155.40	NHS Reference Costs; WAVG of WF01A-D and WF02A-C (127)
Dermatologist telephone appointment	0.192	0.019		£115.44	NHS Reference Costs; WF01C (127)
Dermatologist nurse visit	0.077	0.008		£17.00	PSSRU; per patient contact lasting 15 minutes (128)
GP consultation†	0.000	NA		£42.00	PSSRU; per patient contact lasting 9.22 minutes (128)
A&E visit†	0.000	NA		£220.65	NHS Reference Costs; WAVG of VB06Z-09Z (127)
Psychological support	0.230	0.023		£344.21	NHS Reference Costs; weighted average of WF01A–D (127)

Non-response state					
Dermatologist outpatient consultation	0.419	0.042	Sach et al. (2021) * (TCS + NB-UVB arm) (112)	£155.40	NHS Reference Costs; WAVG of WF01A-D and WF02A-C (127)
Dermatologist telephone appointment	0.005	0.001		£115.44	NHS Reference Costs; WF01C (127)
Dermatologist nurse visit	0.285	0.029		£17.00	PSSRU; per patient contact lasting 15 minutes (128)
GP consultation	0.012	0.001		£42.00	PSSRU; per patient contact lasting 9.22 minutes (128)
A&E visit	0.010	0.001		£220.65	NHS Reference Costs; WAVG of VB06Z-09Z (127)
Psychological support	1.380	0.138	Clinical expert**	£344.21	NHS Reference Costs; weighted average of WF01A–D (127)

Notes: * Resource use items and the corresponding inputs from Sach et al. modified to reflect the resource use items based on the TA681.
** Simple average of inputs suggested by the clinical experts.
† Resource use items considered irrelevant to remission state by the clinical experts.
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.

B.3.5.3 Adverse events

The unit costs for AEs are presented in **Table 42**. Headache is assumed to be self-treated with over-the-counter (OTC) painkillers, hence no cost is considered in the model. The model assumes that patients will seek a dermatologist consultation for acne and pruritis.

Table 42. Unit costs of adverse events

Adverse event	Unit cost	Source
Application site acne	£163.41	NHS Reference Costs (127); consultant-led dermatologist visit (WF01A)
Application site pruritus	£163.41	NHS Reference Costs (127); consultant-led dermatologist visit (WF01A)
Nasopharyngitis	£42.00	PSSRU (128); Unit cost of GP consultation; per surgery consultation lasting 9.22 minutes
Headache	£0.00	Assumed to be self-treated with over-the-counter paracetamol - zero cost applied
Upper respiratory tract infection	£42.00	PSSRU (128); Unit cost of GP consultation; per surgery consultation lasting 9.22 minutes

Abbreviations: GP, general practitioner; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

B.3.5.4 Health-state unit costs and resource use

Please refer to Section B.3.5.2 Disease Management Resource Use and Costs.

B.3.5.5 Miscellaneous unit costs and resource use

No additional miscellaneous unit costs and resource use were included in the model.

B.3.5.6 Severity modifier

A severity modifier is not applicable for the appraisal in question.

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

A summary of the variables applied in the model in the base case analysis is provided in **Table 43.**

Table 43. Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution	Reference to section in submission
Model properties			
Starting age (years)	37.8	Deterministic sensitivity analysis (DSA): Varied ±20% of mean Probabilistic sensitivity analysis (PSA): Normal distribution; standard error from TRuE-V pooled data	Section B.3.3.2 Baseline Patient Characteristics
Proportion female (%)	55.7%	DSA: Varied ±20% of mean PSA: Beta distribution; standard error from TRuE-V pooled data	Section B.3.3.2 Baseline Patient Characteristics
Discount rate costs (%)	3.5%	DSA: Varied to [0, 5] PSA: Not varied	Section B.3.2.3 Features of the economic analysis
Discount rate effects (%)	3.5%	DSA: Varied to [0, 5] PSA: Not varied	Section B.3.2.3 Features of the economic analysis
Time horizon (years)	Lifetime (63)	Scenario analyses	Section B.3.2.3 Features of the economic analysis
Half-cycle correction	Yes	None	Section B.3.2.3 Features of the economic analysis
Patient population	Prior-therapy	None	Section B.3.3.2 Baseline Patient Characteristics
Efficacy			
Initial response definition	F-VASI75	DSA: Varied ±20% of mean PSA: Dirichlet distribution; standard error from TRuE-V pooled data	Section B.3.3.3.1 Treatment initial response probabilities at 24 weeksB.3.3.3.1 Treatment initial response probabilities at 24 weeks
Sustained response for ruxolitinib cream	[redacted]	DSA: Varied 1.96±SE PSA: Beta distribution; standard error from TRuE-V pooled data	Section B.3.3.3.2 Treatment sustained response probabilities at 52

			weeksB.3.3.3.2 Treatment sustained response probabilities at 52 weeks
Sustained response for vehicle cream (OR)	1.0	DSA: Varied ±20% of mean PSA: Log normal distribution; standard error assumed to be 10% of the mean	Section B.3.3.3.2 Treatment sustained response probabilities at 52 weeksB.3.3.3.2 Treatment sustained response probabilities at 52 weeks
Relapse for vehicle cream	[redacted]	DSA: Varied ±20% of mean PSA: Beta distribution; standard error from TRuE-V pooled data	Section B.3.3.3.3 Treatment relapse probabilitiesB.3.3.3.3 Treatment relapse probabilitiesB.3.3.3.3 Treatment relapse probabilities
Relapse for ruxolitinib cream (OR)	1.0	DSA: Varied ±20% of mean PSA: Log normal distribution; standard error assumed to be 10% of the mean	Section B.3.3.3.3 Treatment relapse probabilitiesB.3.3.3.3 Treatment relapse probabilitiesB.3.3.3.3 Treatment relapse probabilities
Regain response for vehicle cream	[redacted]	DSA: Varied ±20% of mean PSA: Beta distribution; standard error from TRuE-V pooled data	Section B.3.3.3.4 Retreatment
Regain response for ruxolitinib cream (OR)	1.0	DSA: Varied ±20% of mean PSA: Log normal distribution; standard error assumed to be 10% of the mean	Section B.3.3.3.4 Retreatment
No regain response for ruxolitinib cream	[redacted]	DSA: Varied ±20% of mean PSA: Beta distribution; standard error from TRuE-V pooled data	Section B.3.3.3.4 Retreatment B.3.3.3.4 Retreatment
No regain response for vehicle cream (OR)	1.0	DSA: Varied ±20% of mean PSA: Log normal distribution; standard error assumed to be 10% of the mean	Section B.3.3.3.4 Retreatment
No response for vehicle cream	[redacted]	DSA: Varied ±20% of mean PSA: Beta distribution; standard error from TRuE-V pooled data	Section B.3.3.3.4 Retreatment

			B.3.3.3.4 Retreatment
No response for ruxolitinib cream (OR)	1.0	DSA: Varied ±20% of mean PSA: Log normal distribution; standard error assumed to be 10% of the mean	Section B.3.3.3.4 Retreatment
Utilities			
Utility data source	Utility mapped from F-VASI (DP: -37.5%)	Scenario Analyses using utilities mapped from VNS and F-VASI (DP: -25%)	Section **Error! Reference source not found.**
Age-related disutility	Yes	None	Section **Error! Reference source not found.Error! Reference source not found.**
Disutility due to AEs	No	None	Section **Error! Reference source not found.Error! Reference source not found.**
Baseline utility value	VitiQoL	None	Section **Error! Reference source not found.**
Costs			
Perspective	NHS and PSS	None	Section B.3.2.3 Features of the economic analysis
Year at which costs in the non-response health state	10	Scenario analyses	Section B.3.5.2 Disease Management Resource Use and Costs

Abbreviations: AE, adverse event; DP, depigmentation; DSA, deterministic sensitivity analysis; EQ-5D, EuroQol-5 Dimension; HSE, health and safety executive; F-VASI, facial vitiligo area scoring index; F-VASI75; 75% or greater improvement from baseline in facial vitiligo area scoring index; HTA, health technology assessment; NICE, National Institute for Health and Care Excellence; OR, odds ratio; PSA, probabilistic sensitivity analysis

B.3.6.2 Assumptions

A list of the assumptions made in the base case analysis and their justifications is provided in **Table 44**. Where appropriate, the exploration of the potential impact of these assumptions in a scenario analysis is noted.

Table 44. List of assumptions for the base case analysis

Assumption	Description/Justification
Sustained response for vehicle cream	Due to a lack of clinical data on sustained response for vehicle cream after 24 weeks, an OR of 1.0 was applied to sustained response for vehicle cream versus ruxolitinib cream in the model to assume equal treatment effects in a conservative scenario.
Re-treatment	Based on the LTE-study data, the model assumed that patients will undergo another line of treatment with ruxolitinib cream/ vehicle cream, following a relapse from the stable health state. This is based on the views of clinical experts who would consider re-treatment with ruxolitinib cream for patients that achieved sustained response at week 52 and would relapse following treatment cessation.
Regain response for ruxolitinib cream in re-treatment phase	Vehicle cream treatment arm data from Cohort A in the LTE study are used when patients relapse and are retreated with ruxolitinib cream; ORs are used to derive ruxolitinib cream data with a conservative assumption of equal treatment effect (i.e., an OR of 1.0 is applied).
No regain response for vehicle cream in re-treatment phase	Ruxolitinib cream shift summary of F-VASI from Week 52 to Week 104 data from Cohort B in the LTE study are used; ORs are used to derive vehicle cream data with a conservative assumption of equal treatment effect (i.e., an OR of 1.0 is applied).
No response in re-treatment phase	In the absence of relapse data for previously retreated patients that had achieved F-VASI90 and given that the same F-VASI definitions are used for both transitions, relapse data are used as a proxy for the 'no response' transition.
Non-response state	Patients in the non-response state remain in that state until the end of model simulation or death. This reflects that patients who have failed treatment with ruxolitinib cream or vehicle cream may go on to receive a basket of BSC therapies.
Adverse events	Assumed to remain constant over the treatment duration. AE rates are based on the 24 weeks data cut of TRuE-V pooled data to reflect also the vehicle cream arm. Since mild AEs were reported in the TRuE-V studies, disutility due to AEs is not included in the model, in line with TA534 (117) and TA681 (118) for AD.
Age-related disutility	Based on the NICE DSU report on estimating EQ-5D by age and sex, published by Hernández Alava et al. 2022 (145). Based on the NICE DSU report on estimating EQ-5D by age and sex, published by Hernández Alava et al. 2022 (145).
Efficacy during initial period	Efficacy in the initial period is assumed to occur at the end of the initial period, so only patients who enter the maintenance period benefit from treatment. A similar assumption was made in TA681 (118).
Discontinuation rate of vehicle cream during maintenance	Patients who were initially treated with vehicle cream switched to ruxolitinib cream at week 24; hence, the discontinuation rate of vehicle cream during the maintenance period was calculated based on patients treated with vehicle cream until week 24 who discontinued treatment with ruxolitinib cream between week 24 and week 52.

Relapse rate for vehicle cream	Assumed equal to relapse for ruxolitinib cream. Relapse is applied in the stable state where patients are off-treatment, hence it is assumed to not be treatment-specific.
Costing approach for vehicle cream	Vehicle cream cost assumed to be equal to sunscreen cost, based on clinical experts' opinion, as patients with vitiligo normally use sunscreen.
Concomitant therapy composition	In line with clinical experts' suggestions, concomitant therapy includes vitamin D supplements, camouflage, fixing powder and sunscreen. Concomitant therapy is assumed not to be associated with any effectiveness or HRQoL benefit.
BSC composition	BSC involves tacrolimus ointment, mometasone ointment, oral dexamethasone, camouflage, fixing powder, sunscreen and NB-UVB, based on the proportions of patients on each treatment from the VALIANT study (**Figure 21**) (131), along with vitamin D supplements, in line with clinical expert suggestions. BSC is assumed to not be associated with any effectiveness or HRQoL benefit.
Duration of costs applied in non-response	Disease management costs in the non-response health state are assumed to apply for the first 10 years only since the start of model simulation following input from clinical experts who stated that patients would consider discontinuing treatment and visits to the healthcare specialists after a certain period without any improvement. This is due to treatment fatigue that patients experience and patient choice varies with time (122).
Concomitant therapy	Resource use of concomitant therapy (vitamin D supplement, camouflage, fixing powder and sunscreen) is based on the simple average of clinical experts' suggestions.
BSC resource use	Resource use of vitamin D supplement, camouflage, fixing powder and sunscreen in the non-response health state is based on the simple average of clinical experts' suggestions.
Resource use items	Resource use items and estimates were obtained from Sach et al. (112). However, the resource use categories from Sach et al. were modified to reflect the resource use categories from TA681 (118). The costing categories presented in Sach et al. (2021) were combined into six costing categories: dermatologist outpatient consultation, dermatologist telephone appointment, dermatologist nurse visit, general practitioner consultation (GP) and accident and emergency (A&E) visit. Clinicians suggested removing hospitalisations and including psychological support as an additional costing category.
Resource use frequency across health states	For initial period, maintenance and re-treated health states, the resource use for all items except psychological support is based on based on the TCS arm, as reported in Sach et al (112). Resource use of psychological support is based on the simple average of clinical expert suggestions. For the stable and stable re-treated states, resource use for all items is based on the simple average of clinical experts' suggestions. For the non-response health state, the resource use for all items except psychological support is based on the combination arm (NB-UVB + TCS), as reported in Sach et al. (112). Resource use of psychological support is based on the simple average of clinical expert suggestions.

Abbreviations: AD, atopic dermatitis; AE, adverse event; BSA, body surface area; BSC, best supportive care; DLQI, dermatology life quality index; DLQI≥4, improvement of ≥4 from baseline in DLQI; DSU, Decision Support Unit; EQ-5D-3L, EuroQol-5 Dimension-3 Level; F-VASI, facial vitiligo area scoring index; F-VASI50, 50% or greater improvement from baseline in F-VASI; F-VASI75, 75% or greater improvement from baseline in F-VASI; F-VASI90, 90% or greater improvement from baseline in F-VASI;

HRQoL, health-related quality of life; NB-UVB, narrowband ultraviolet B; NICE, National Institute for Health and Care Excellence; OR, odds ratio; TA, technology appraisal; TCS, topical corticosteroid; VNS, vitiligo noticeability scale.

B.3.7 Base case results

B.3.7.1 Base case incremental cost-effectiveness analysis results

The base case probabilistic cost-effectiveness results are presented in **Table 45**. For all analyses, ruxolitinib cream was considered at its confidential PAS price ([redacted]). When compared to vehicle cream, ruxolitinib cream produces an additional [redacted] QALYs with an incremental cost of [redacted], resulting in an ICER of £14,676. On average, patients on ruxolitinib cream spent 0.503 years in F-VASI90 (i.e., on maintenance and stable) compared with 0.042 years in patients on vehicle cream. These results indicate that ruxolitinib cream is cost-effective versus vehicle cream at a cost-effectiveness threshold of £20,000 for the base case population of adult and adolescent patients >12 years of age with NSV that have received prior therapy.

Table 45. Base case summary results at PAS price, prior therapy population

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)
Vehicle cream	0.042	[redacted]		-	-	-	-
Ruxolitinib cream	0.503	[redacted]	[redacted]	0.461	[redacted]	[redacted]	£14,676

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

B.3.8 Sensitivity analyses

DSA and PSA were conducted to test the robustness of the model to the uncertainties within the model parameters. These are presented in Sections

B.3.8.1 Probabilistic sensitivity analysis and B.3.8.2 Deterministic sensitivity analysis, respectively. The scenario analyses undertaken to explore the uncertainty around model assumptions are presented in Section B.3.8.3 Scenario analysis.

B.3.8.1 Probabilistic sensitivity analysis

Joint parameter uncertainty was tested through PSA, in which all parameters are assigned distributions and varied jointly. Two thousand Monte Carlo simulations were recorded and plotted on the cost-effectiveness plane shown in **Figure 22** below. The results of the PSA were found to be congruent with the base case results. Results showed that [redacted]% of samples lie in the north-east quadrant where the target intervention is more costly and more effective compared with vehicle cream, with [redacted]% of samples lying in the south-east quadrant where ruxolitinib cream is dominant over vehicle cream. 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 23** below.

Figure 22. Cost-effectiveness plane for ruxolitinib cream compared with vehicle cream at PAS price

Figure 23. Cost-effectiveness acceptability curve for ruxolitinib cream compared with vehicle cream at PAS price

Convergence testing showed that convergence was achieved as presented in the convergence plot for net monetary benefit (NMB) below (**Figure 24**).

Figure 24. Convergence plot for net monetary benefit at PAS price

B.3.8.2 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 25**). The most influential parameters for the analysis of ruxolitinib cream versus vehicle cream are the initial F-VASI75-89 response rate for vehicle cream and initial F-VASI90 response rate for ruxolitinib cream at week 24. NB-UVB related parameters, such as the number of sessions and percentage of patients receiving NB-UVB were found to have a moderate impact on the ICER. Utility values for F-VASI75-89, F-VASI90 and non-response states were shown to have minimal impact on the ICER.

Figure 25. Tornado diagram for ruxolitinib cream compared with vehicle cream at PAS price

B.3.8.3 Scenario analysis

Uncertainty around key modelling elements were tested in scenario analyses in which model assumptions and parameters were altered. The scenario analyses carried out are presented in **Table 46** and the results of these analyses are presented below in **Table 47** for the confidential PAS price.

Table 46. Overview of model scenario analyses

No	Model scenario	Base Case	Description/Justification
1	Utility data source: F-VASI (DP: -25%)	Utility data source: F-VASI (DP: -37.5%)	This scenario explores the impact of utilising alternative bandings in the F-VASI mapping algorithm. Depigmentation categorisation I: Percentage change of -25% (i.e., all patients with depigmentation were truncated to having skin pigmentation loss not greater than 25%) [DP: -25%] (Section **Error! Reference source not found.**
2	Utility data source: VNS	Utility data source: F-VASI (DP: -37.5%)	VNS was the secondary endpoint in the TRuE-V studies (93). As such, mapping from this endpoint was considered for scenario analyses.
3	Model time horizon: 10 years	Model time horizon: Lifetime (63 years)	This scenario explores the impact of a shorter time horizon in the model.
4	Stop costs in the non-response state: 5 years	Stop costs in the non-response state: 10 years	This scenario explores the impact of varying the length of time costs are incurred in the non-response state. This aligns with clinical feedback where clinicians noted that patients experience treatment fatigue and patient choice varies over time (122).
5	Stop costs in the non-response state: Lifetime	Stop costs in the non-response state: 10 years	This scenario explores the impact of varying the length of time costs are incurred in the non-response state. This aligns with clinical feedback where clinicians noted that patients experience treatment fatigue and patient choice varies over time (122).
6	Overall population	Prior therapy sub-group	This scenario explores the impact of assessing the overall population recruited in the TRuE-V studies.
7	Patients from overall population with Fitzpatrick skin type IV-VI	Prior therapy sub-group	The Fitzpatrick IV-VI categorisation was chosen as darker skin types are associated with a greater patient burden (18) including use of a significantly greater number of treatments (132). This categorisation has been used in a recent study which assessed the importance of facial involvement for patients (56).

Abbreviations: DP, depigmentation; F-VASI, facial vitiligo area scoring index; VNS, vitiligo noticeability scale.

Table 47. Summary of key cost-effectiveness results from scenario analyses at PAS price

No	Model scenario	Treatment	Total costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER vs vehicle cream
1	Utility data source: F-VASI (DP: -25%)	Vehicle cream	[redacted]	[redacted]	-	-	-
		Ruxolitinib cream	[redacted]	[redacted]	[redacted]	[redacted]	£20,348
2	Utility data source: VNS	Vehicle cream	[redacted]	[redacted]	-	-	-
		Ruxolitinib cream	[redacted]	[redacted]	[redacted]	[redacted]	£398,929
3	Model time horizon: 10 years	Vehicle cream	[redacted]	[redacted]	-	-	-
		Ruxolitinib cream	[redacted]	[redacted]	[redacted]	[redacted]	£5,687
4	Costs in the non-response state stop at: 5 years	Vehicle cream	[redacted]	[redacted]			
		Ruxolitinib cream	[redacted]	[redacted]	[redacted]	[redacted]	£39,272
5	Costs in the non-response state stop at: Lifetime	Vehicle cream	[redacted]	[redacted]	-	-	-
		Ruxolitinib cream	[redacted]	[redacted]	[redacted]	[redacted]	£3,894
6	Population: Overall	Vehicle cream	[redacted]	[redacted]	-	-	-
		Ruxolitinib cream	[redacted]	[redacted]	[redacted]	[redacted]	£19,179
7	Population: Fitzpatrick skin type IV-VI	Vehicle cream	[redacted]	[redacted]	-	-	-
		Ruxolitinib cream	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: DP, depigmentation; F-VASI, facial vitiligo area scoring index; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

B.3.8.4 Summary of sensitivity and scenario analyses results

The sensitivity analysis results indicate that the base case cost-effectiveness outcomes display minimal variation when considering the combined distributional uncertainty across model parameters. The probabilistic base case analysis findings demonstrate robustness in the analysis of ruxolitinib cream compared to vehicle cream. The DSA reveals that the most influential parameters driving the model for the comparison of ruxolitinib cream with vehicle cream include the initial F-VASI75 response rate for vehicle cream, the initial F-VASI90 response rate for ruxolitinib cream, NB-UVB related inputs (number of sessions and patient proportions in BSC) and the discontinuation rates in the maintenance period for vehicle cream.

The majority of the scenario analyses conducted using the confidential PAS price exhibit limited variation in the modelling approach, with the exception of VNS as the source of utility data. In one scenario, ruxolitinib cream was dominant over vehicle cream (scenario 7), in three scenarios (scenarios 3, 5 and 6), ruxolitinib cream versus vehicle cream was associated with an ICER of less than £20,000 per QALY gained, and in another scenario (scenario 1) ruxolitinib cream versus vehicle cream was associated with an ICER of less than £30,000 per QALY gained. Collectively, these findings demonstrate the model's robustness to variation in key modelling assumptions.

B.3.9 Subgroup analysis

No further subgroup analyses were performed beyond those listed above.

B.3.10 Benefits not captured in the QALY calculation

EQ-5D may not fully capture the HRQoL impairment of patients living with vitiligo. This lack of content validity of the EQ-5D instrument was substantiated by a large ceiling effect observed in the EQ-5D data at baseline from the HI-Light trial, whereby many patients at baseline reported almost “perfect health” on the EQ-5D instrument and therefore were unable to report an improvement from treatment in a responder analysis. The utility estimates derived from disease-specific outcome measures from the TRuE-V studies to EQ-5D are likely to be affected in the same manner (112).

B.3.11 Validation

The model was developed in line with best modelling practices (146) and in alignment with NICE preferred methods. The model was developed in line with best modelling practices (146) and in alignment with NICE preferred methods. The model aligns with the NICE reference case (116).

As noted in Section B.3.2.2 Model structure, not only were relevant previous submissions in dermatology conditions reviewed, but extensive validation was also conducted as part of the development of the cost-effectiveness model. This included input from clinicians and health economists during the conceptualisation of the model structure, validation during model development and a final validation once the model had been finalised. Validation was also conducted on the clinical and economic inputs with expertise from clinicians and health economists.

Following the finalisation of the model, a full quality control assessment was conducted. This included a review of all calculations and inputs used in the model by independent internal and external third-party modellers. The internal review followed a technical checklist which guided the reviewer in the review of formulae, equations, cross-check of inputs (clinical, resource use, utility), VBA coding and face validity of results. Stress tests were also conducted to ensure that results returned were robust to extreme values. The results of the quality control are provided in Appendix N.

B.3.12 Interpretation and conclusions of economic evidence

B.3.12.1 Strengths and Limitations

The cost-effectiveness analysis described in this submission is a robust and defensible analysis which accounts for the clinical pathway of care that patients would experience and utilises the most appropriate available data. Overall limitations in this analysis are driven by the limited research (including but not limited to randomised controlled and structured research) that exists, since no existing treatments have received a regulatory licence for the treatment of vitiligo. Ruxolitinib cream is the first licenced treatment for people over 12 years for NSV with facial involvement.

In the absence of previously published cost-effectiveness models in vitiligo, the cost-effectiveness model was developed following a review of previous submissions (117-119) in other dermatological conditions such as psoriasis and atopic dermatitis. These

previous submissions helped inform an initial model conceptualisation where a Markov structure accounting for the chronic nature and natural history of vitiligo was deemed appropriate. A review of previous submissions in dermatology also ensured that this submission considered potentially relevant key discussion points. The lack of submissions in vitiligo was mitigated by extensive clinical validation meetings with dermatology experts and one health economist based in the UK (121, 122). These covered a wide range of topics including the typical patient treatment pathway, model structure, and model inputs as well as assumptions. This meant that the model structure accounted for the patient pathway and all inputs and assumptions made were clinically plausible. Where treatment-specific data were unavailable, such as in the modelling of re-treatment, conservative data choices and assumptions were taken to reduce the potential for a biased analysis. These included using data on relapse to inform loss of re-gained response and assuming equal treatment effects.

A key strength of the analysis is that clinical data are based on two robust Phase III trials (2, 3) and a long-term extension study (4) reporting data representative of the English population, meaning that the results of the cost-effectiveness analysis are generalisable to the NHS setting. Although the trial results are generalisable, EQ-5D data were not collected as it is understood that this measure does not capture items of relevance in vitiligo as evidenced by a large ceiling effect being observed in a UK-based clinical trial (112). Mapping algorithms based on the HI-Light study, a pragmatic RCT in vitiligo conducted in the UK, were developed following statistical best practice and the latest guidance from NICE (140) on mapping. The HI-Light population is broadly similar in terms of clinical and demographic characteristics to that of the TRuE-V population and as HI-Light is a pragmatic trial, data are reflective of real-world practice (2, 3, 110). The measurement of VASI between HI-Light and the TRuE-V studies differed slightly, although in both trials the impact of vitiligo on the face was captured in an almost identical way. It should be highlighted that the categorisation of repigmentation (for RPS) in HI-Light is consistent with that of F-VASI in the TRuE-V studies and a standard approach for the measurement of repigmentation was used in HI-Light (82). Further, adjustments were made to VASI categories in the TRuE-V studies to reflect repigmentation versus depigmentation (126). Finally, the analysis highlighted a high correlation between VASI and EQ-5D utilities (126). In the absence of other suitable alternatives, this was deemed the most appropriate data source to

use. As such, the utilities used in the presented cost-effectiveness analysis are not only statistically robust, but RPS can be considered an appropriate proxy for F-VASI.

Another area of uncertainty is the length of time patients would receive BSC following treatment with ruxolitinib cream as these data simply do not exist, which is the reason why the base case made a conservative assumption of 10 years since the model start, with lower and higher variations tested in the scenario analyses. These indicated that lifetime use of BSC is indeed cost-effective with an ICER of £3,894 but that a 5-year stopping rule gives an ICER of £39,272. In terms of the utility-based scenario analyses, using F-VASI (DP: -25%) gives an ICER of £20,348 whilst VNS-based utilities is £398,929. However, it should be noted that the VNS is a subjective measure of the cosmetic acceptability of repigmentation (114) and does not perform as well as the F-VASI mapping algorithm (125).

B.3.12.2 Conclusion

The cost-effectiveness analysis presented in this submission addresses a sub-population of the licensed population, that is, for patients who have not responded to TCS or TCI alone, or for whom TCS or TCI are contraindicated, not tolerated or otherwise medically inadvisable. The robust methodologies and techniques used in the analysis ensure that its results are viable and generalisable to an NHS setting and that ruxolitinib cream is 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 over [ID3998]

Summary of Information for Patients (SIP)

August 2023

File name	Version	Contains confidential information	Date
ID3998_Ruxolitinib cream_STA_Summary of information for patients (SIP)	V1.0	Yes/no	10th August 2023

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

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

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

SECTION 1: Submission summary

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

Generic name: Ruxolitinib 1.5% cream (1) **Brand name:** Opzelura® (1)

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

This submission focuses on patients from 12 years of age with non-segmental vitiligo that affects the patients' face, for whom some other treatments have not worked, or the patients have not been able to tolerate them.

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

The Medicines and Healthcare Products Regulatory Agency (MHRA) is the government agency that is responsible for regulating medicines in the UK. Ruxolitinib cream received approval from the MHRA on 4th July 2023 for the treatment of patients from 12 years of age with non-segmental vitiligo that affects the patients' face (1).

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

At the time of submission, Incyte has not provided any financial support or donation to patient organisations in this area. As part of Incyte's engagement in this area, Incyte has worked with patients at a European level who will be reimbursed for their time at a fair market value. When working with patients or patient organisations, Incyte follows all relevant regulations and legislation to ensure that they remain independent.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

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

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

What is non-segmental vitiligo?

Vitiligo is a long-term (chronic) autoimmune condition, in which the body's immune system attacks the cells that produce the skin pigment melanin, which leads to patches of pale pink or white skin which are prone to sun damage (2-5). Vitiligo can affect any area of the skin. The most commonly affected areas include the face, hands and neck. There are two main types of vitiligo, namely non-segmental vitiligo (NSV) and segmental vitiligo. When a person has NSV, patches tend to appear on both sides of the body, like both hands or both knees, whereas segmental vitiligo causes the skin to lose colour on one side or part of the body only (6).

How many people get non-segmental vitiligo?

NSV is the most common type of vitiligo, affecting eight in ten people with vitiligo (7). It may appear early (<12 years of age), and it peaks at around 30 years of age (3). Based on 2020 figures, it is estimated that approximately 570,000 people in England and Wales have NSV (8).

What is the impact of non-segmental vitiligo on patients' quality of life?

Patients with vitiligo experience a high burden on their quality of life (9, 10), especially when it occurs in visible areas, such as the face and hands (11-13). Vitiligo can have a substantial psychological burden on patients (14-16), which may result in the need for medication, hospitalisation for mental health disorders, and reduced work productivity (17-19).

Incyte funded a study called the Vitiligo And Life Impact Among International communities (VALIANT). The study consisted of a 25/30-minute online survey designed to understand the impact and burden of vitiligo on patients' quality of life from the perspective of both patients and healthcare professionals (HCPs). The survey was completed by 3,541 patients and 1,203 HCPs across 17 countries (20). In this study, more than half (54.2%) of patients in the UK reported symptoms of moderate-to-severe depression. Negative effects on daily activities are greater and rates of moderate-to-severe depression are higher in patients with a greater body surface area affected, those with facial lesions, and those with a darker skin tone (20).

NICE is assessing the use of ruxolitinib cream for the treatment of patients from 12 years of age with NSV that affects the patients' face (1).

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

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

How is non-segmental vitiligo diagnosed?

A doctor can diagnose non-segmental vitiligo (NSV) based on a physical examination of the affected areas of the skin and the patient's clinical history (3, 21). The doctor may also ask if there is a history of vitiligo or other autoimmune conditions in the patient's family (3, 21).

The doctor may use an ultraviolet (UV) lamp called a Wood's lamp to look at the patient's skin in more detail. The patches of vitiligo can be seen more easily under UV light, which can help the doctor distinguish vitiligo from other skin conditions and confirm the diagnosis (3, 21).

No specific diagnostic tests are required with ruxolitinib cream.

2c) Current treatment options:

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

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

What treatment guidelines are available for patients with vitiligo in the UK?

Guidelines for treating people with vitiligo are issued by the British Association of Dermatologists (BAD) (22). The guidelines recommend talking to patients about their experiences of living with vitiligo, and where appropriate, referring patients to supportive mental health services (22).

What are the current treatment options?

White patches caused by vitiligo are usually permanent, although treatment options are available to reduce their appearance. For small patches, camouflage cream can be used to cover them up.

In addition, there are treatments that can be used to restore some pigment. These treatments have not specifically been approved for use in vitiligo (off-label), they include treatments applied on the skin (topical treatments), light therapy (phototherapy), laser therapy, and vitamin D. Sometimes, a number of these treatments are used in combination.

Options for initial therapy

Only topical treatments are considered for initial therapy (22). Topical corticosteroids are recommended once daily for up to 2 months, with topical tacrolimus 0.1% ointment as an option for facial areas (22). To minimise the risk of side effects with the use of topical corticosteroids, these could be recommended in alternating weeks with topical tacrolimus (22).

Other treatment options

Patients whose vitiligo does not respond to treatment applied on the skin (topical treatment) and those with vitiligo that is getting worse may be offered light therapy or oral betamethasone (a

steroid), respectively, in addition to topical treatment (22). Oral betamethasone is recommended for a maximum of 3 months.

Laser treatment (excimer laser) in combination with a topical calcineurin inhibitor (TCI) are considered for localised vitiligo, while surgical therapies are reserved for those in which the vitiligo is stable (not getting worse or better). CO2 laser in combination with 5-fluorouracil (a drug that increases sensitivity to light therapy) is considered in adults with non-segmental vitiligo (NSV) on hands and feet, and removing the remaining pigment (depigmentation) is considered for patients with more extensive disease on visible areas (22).

What are the limitations of the current treatment options?

Treatment options that have not specifically been approved for use in vitiligo (off-label treatments), such as topical steroids, topical calcineurin inhibitors and light therapy (2, 21, 23), have well-known risks and limitations for their use in vitiligo, including limited evidence for efficacy and long-term safety (24, 25), and limited tolerability (23, 26-29).

Access to light therapy for patients with vitiligo varies across regions in the country. Currently in the National Health Service (NHS), dermatology waiting lists vary between 12-24 months for general dermatology clinics (30). In addition, once seen in secondary care, many patients with vitiligo are unable to start light therapy either due to long NHS waiting lists (over one year at some centres, following first assessment by a dermatologist) for this treatment option, and/or personal time constraints (i.e., the need to attend three times a week for 9-12 months) (30). Furthermore, many dermatology departments offer light therapy to a small group of patients with vitiligo due to the prolonged course of treatment. As such, patients with other dermatological diseases (such as eczema or psoriasis) who usually require shorter courses are prioritised instead (30).

Who is ruxolitinib cream recommended for?

Ruxolitinib cream is anticipated to be positioned as a treatment option for patients from 12 years of age with non-segmental vitiligo (NSV) that affects their face, for whom the disease has not responded to treatment with topical corticosteroids (TCS) or topical calcineurin inhibitors (TCI), if they do not tolerate TCS or TCI, or for whom TCS or TCI are advised against by the patient's doctor.

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

Context:

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

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

Patient-based evidence (PBE) about living with the condition was collected as part of the Vitiligo And Life Impact Among International communities (VALIANT) study that was funded by Incyte.

Description of the VALIANT study

The study consisted of a 25/30-minute online survey designed to understand the impact and burden of vitiligo on patients' quality of life from the perspective of both patients and healthcare professionals (HCPs). The survey was completed by 3,541 patients and 1,203 HCPs across 17 countries (20).

Results from the VALIANT study

In this study, more than half (54.2%) of patients in the UK reported symptoms of moderate-to-severe depression. Negative effects on daily activities are greater and rates of moderate-to-severe depression are higher in patients with a greater body surface area affected, those with facial lesions, and those with a darker skin tone (20).

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

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

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

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

Vitiligo is understood to be a condition in which a person's overactive immune system activates a signal called the JAK-STAT pathway. Once this pathway is activated within their immune system, pigment-producing cells in the skin called melanocytes are destroyed, leading to a loss of the skin's colour. Ruxolitinib cream is currently the only approved treatment that targets this JAK-STAT pathway and in turn helps reduce melanocyte destruction, restoring a favourable environment in the skin where repigmentation can take place again over time (5).

The summary of product characteristics (SmPC) and patient information leaflet (PIL) can be downloaded here.

3b) Combinations with other medicines

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

- Yes / No

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

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

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

Ruxolitinib cream is not intended to be used in combination with other medicines, however, several therapies may be taken/applied at the same time as ruxolitinib cream, including vitamin D supplement, camouflage, fixing powder and sunscreen.

3c) Administration and dosing

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

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

How is ruxolitinib cream applied?

Patients should apply ruxolitinib cream twice daily to the affected areas of the skin (5). A thin layer of ruxolitinib cream should be applied to the affected areas of the skin. Patients should wait at least 8 hours between applications. The cream should not be used on more than 10% (one tenth) of the body. This surface area represents the equivalent to ten times the size of an open hand (5).

Patients should not apply the cream to skin surfaces other than the ones instructed by their doctor. Patients should wash their hands after applying the medicine unless their hands are being treated. If someone applies this medicine to the patient, they should wash their hands after application. Patients should avoid washing the treated skin for at least 2 hours after application of ruxolitinib cream (5).

3d) Current clinical trials

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

Clinical studies of ruxolitinib cream in non-segmental vitiligo (NSV)

Ruxolitinib cream was studied across North America and Europe in two identically designed clinical trials (which we refer to as TRuE-V1 and TRuE-V2) (31-35), and an additional clinical study in which patients who completed either TRuE-V1 or TRuE-V2 were followed over a longer period of time (TRuE-V LTE) (36, 37).

TRuE-V1 and TRuE-V2

Participants in TRuE-V1 and TRuE-V2 included over 650 people, both males and females with non-segmental vitiligo (NSV) across a range of skin tones and races, who were aged 12 years and older and had vitiligo affecting up to 10% (one tenth) of their body surface area. Patients were randomly assigned to apply either ruxolitinib cream or a cream with no active ingredient (which we refer to as vehicle cream) for 6 months to all affected areas on the face and body. After 6 months, patients from both groups applied ruxolitinib for another 6 months (31-35). Details about the TRuE-V1 study are available at: https://www.clinicaltrials.gov/study/NCT04052425. Details about the TRuE-V2 study are available at: https://www.clinicaltrials.gov/study/NCT04057573.

TRuE-V LTE

TRuE-V LTE enrolled eligible patients who completed either TRuE-V1 or TRuE-V2 (36, 37). Details about the TRuE-V LTE study are available at https://clinicaltrials.gov/study/NCT04530344.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

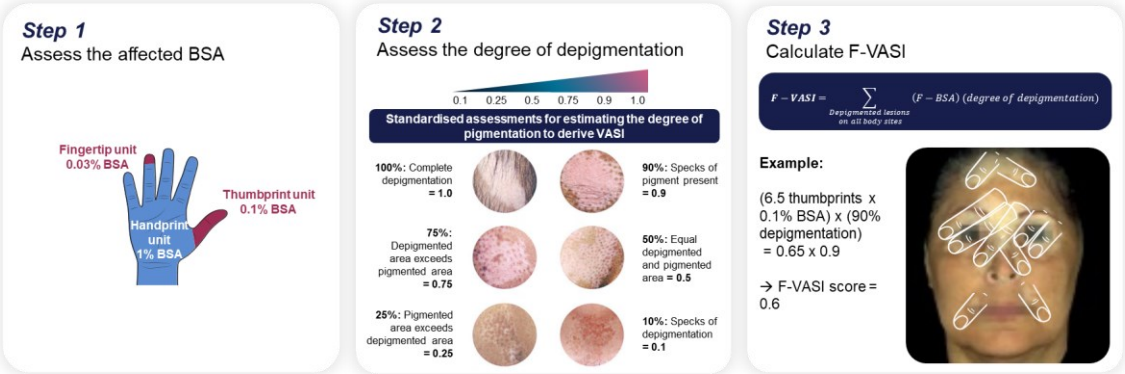
In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Results of the TRuE-V1 and TRuE-V2 studies after 24 weeks and 52 weeks of treatment with ruxolitinib cream showed significant repigmentation of the areas that are affected by vitiligo, both on the face and on other parts of the body (31).

A. Facial repigmentation results

F-VASI is a reliable and validated tool for assessing repigmentation on the patient's face (38). The diagram below explains how the F-VASI score is calculated.

Calculating F-VASI



Significant improvement in F-VASI75 was seen at Week 24

In the analysis combining results of the two identical clinical studies (TRuE-V1 and TRuE-V2), around one in three patients (30.7%) who used ruxolitinib cream saw at least 75% improvement in their facial vitiligo (F-VASI75) after 6 months of treatment, which was significantly better than in patients who received the cream without an active ingredient (vehicle cream) (31).

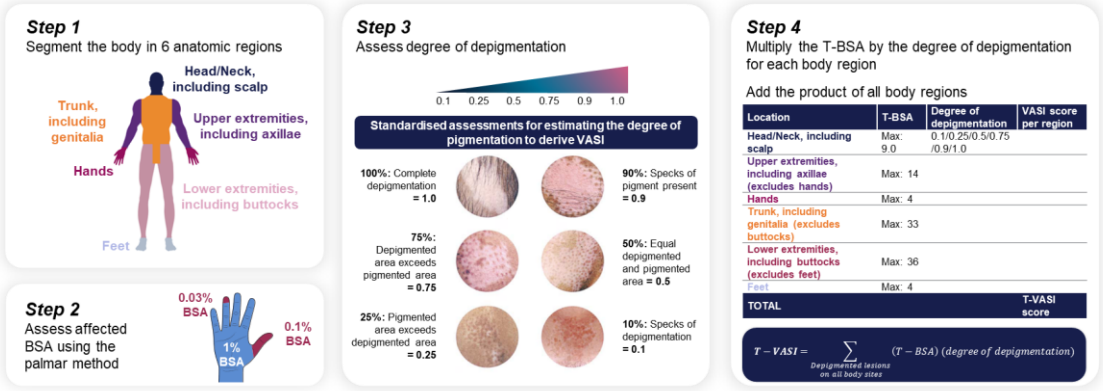
Significant improvement in F-VASI50 and F-VASI90 was seen at Week 24

In the analysis combining results of the two identical clinical studies (TRuE-V1 and TRuE-V2), around one in two patients (51.7%) who used ruxolitinib cream saw at least 50% improvement in their facial vitiligo after 6 months of treatment, which was significantly better than in patients who received the cream without an active ingredient (vehicle cream). Similarly, around one in six patients (16%) who received ruxolitinib saw at least 90% improvement in their facial vitiligo after 6 months of treatment, which was significantly better than in patients who received the cream without an active ingredient (vehicle cream) (31).

B. Body repigmentation results

Total body vitiligo area scoring index (T-VASI) is a reliable tool for assessing repigmentation on the patient's body (38).

Calculating T-VASI



Significant improvement in T-VASI50 was seen at Week 24

In the analysis combining results of the two identical clinical studies (TRuE-V1 and TRuE-V2), around one in five patients who received ruxolitinib cream (21.9%) saw at least 50% improvement in their total body vitiligo (T-VASI50) after 6 months of treatment. This was significantly better than in patients who received the cream without an active ingredient (vehicle cream) (31).

C. Vitiligo noticeability scale (VNS):

VNS is a patient-reported measure of vitiligo treatment success that measures how noticeable vitiligo is after treatment. Patients provide responses as: (1) More noticeable, (2) As noticeable, (3) Slightly less noticeable, (4) A lot less noticeable, and (5) No longer noticeable, in relation to vitiligo. Scores of 4 or 5 represent treatment success.

In the analysis combining the results from TRuE-V1 and TRuE-V2, the proportion of patients reporting a VNS score of 4 or 5 increased from Week 12 to Week 24 in the ruxolitinib cream treatment group, while remaining low in the vehicle group. The proportion of patients reporting a VNS score of 4 or 5 was larger in the ruxolitinib cream group (22.5%) compared to the vehicle group (4.2%) (31). At Week 52, 127/350 patients (36.3%) achieved a VNS response of 4 or 5 (31).

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

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

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

The impact of ruxolitinib cream on the quality of life of patients

The TRuE-V1 and TRuE-V2 clinical trials measured patients' health related quality of life (HRQoL) using the dermatology life quality index (DLQI) and the vitiligo-specific quality of life instrument (VitiQoL) questionnaires (31-33).

DLQI is a 10-item questionnaire concerning patients' perception of the impact of skin diseases on different aspects of their health-related quality of life over the last week. Children DLQI (CDLQI) is a similar questionnaire designed to measure the impact of any skin disease on the lives of children.

VitiQoL is a 15-item quality-of-life assessment questionnaire that asks patients with vitiligo to rate various aspects of their condition during the past month using a 7-point scale ("Not at all" to "All of the time"), with high scores indicating worse quality of life (32, 33, 39).

Results from both TRuE-V1 and TRuE-V2 showed numerical differences in DLQI and VitiQoL between patients who received ruxolitinib cream and those who received a cream with no active ingredient (vehicle cream), but no statistically significant differences were found (31).

EuroQol 5 Dimension 5 Level (EQ-5D) is the tool that is preferred by NICE to measure the health-related quality of life (HRQoL) in adults. However, in the TRuE-V clinical trials, EQ-5D data was not collected. In order to capture the HRQoL benefits of ruxolitinib cream in vitiligo patients, Incyte used the latest mapping algorithms to estimate EQ-5D data based on other specific measures related to vitiligo, such as vitiligo assessment scoring index (VASI) and vitiligo noticeability scale (VNS). After testing different algorithms, the one based on VASI followed by VNS showed the best statistical performance, providing valuable insights into how the treatment affects patients' quality of life.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Like all medicines, ruxolitinib cream can cause side effects, although not everybody experiences them. Up to 1 in 10 patients who used ruxolitinib cream reported acne (1, 5).

Ruxolitinib cream has been shown to be well-tolerated by patients over a long period of time in two Phase III studies. In patients aged 12 years or older, nearly eight out of ten patients continued to use ruxolitinib cream after a year (31, 34, 35). Unwanted reactions (adverse events) were mostly of a mild or moderate nature. When adjusted for exposure time (i.e., time patients were exposed to ruxolitinib cream), the rate of adverse events was lower in patients who applied ruxolitinib cream than in patients who applied vehicle cream (40).

3h) Summary of key benefits of treatment for patients

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

Ruxolitinib cream is **the first and only** treatment to be licensed for treatment of adults and adolescents with non-segmental vitiligo (NSV) (1).

It is a **steroid-free, topical cream** that patients can apply by themselves (1, 5).

It was shown to help significantly restore some skin colour over time in patients with NSV aged 12 years or older (31).

Around a third of patients with NSV from two Phase 3 clinical trials saw **at least 75% improvement** in facial repigmentation after 6 months of treatment (31).

Half of patients with NSV from two Phase 3 clinical trials saw **at least 50% improvement** in facial repigmentation after 6 months of treatment (31).

Around one in five patients with NSV from two Phase 3 clinical trials saw **at least 50% improvement** in their total body repigmentation after 6 months of treatment (31).

Ruxolitinib cream was **well tolerated** by patients in long-term Phase III clinical studies (31)

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

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

- Although ruxolitinib cream is licensed for non-segmental vitiligo (NSV) (1), which accounts for around 80% of patients with vitiligo (7), it is not licensed for patients with segmental vitiligo.
- Ruxolitinib cream is not for use in the eyes, inside the mouth or in the vagina. In cases of accidental exposure in the eyes or mucous membranes, the cream should be thoroughly wiped off and/or rinsed with water (1).
- Only up to 10% (one tenth) of the patient's body surface area may be treated at a time.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Healthcare administrators need to get the best value from their limited budgets. To do this, they want to know whether a new medicine provides 'good value for money' compared to existing medicines. They will look at the costs of the new medicine and how the health of patients is likely to improve if they take it. The pharmaceutical company that develops the medicines provides this information to healthcare administrators using a health economic model. The pharmaceutical company uses the health economic model to perform an analysis which compares the costs and benefits of the new treatment (ruxolitinib cream) with the comparator (a cream without an active ingredient, which we refer to as "vehicle cream").

The model reflects the experience of patients living with non-segmental vitiligo

Informed by a literature review of published cost-effectiveness models in vitiligo and other long-term (chronic) skin conditions as well as several interviews with clinical experts in vitiligo, a health economic model was developed to capture the costs and benefits of introducing ruxolitinib cream into the current care pathway. This model was developed to accurately reflect the experience of

patients living with non-segmental vitiligo (NSV) in England, and uses evidence from clinical trials of ruxolitinib cream (i.e., TRuE-V 1, TRuE-V2 and TRuE-V LTE).

A cost-effectiveness model was created to capture the costs and benefits of treatment with ruxolitinib cream versus vehicle cream over a lifetime in the target population. Vehicle cream was selected as comparator to reflect the anticipated use of ruxolitinib in the care pathway (i.e., after topical corticosteroids (TCS) or topical calcineurin inhibitors (TCI), prior to light therapy [phototherapy]) and to utilise the direct evidence from the randomised clinical trials. Comparisons against existing off-label treatments such as TCS, TCI and light therapy were also explored but not possible due to the limited evidence base of these treatments.

Conclusion

As the first licensed treatment for NSV, ruxolitinib cream addresses an unmet need by offering an effective treatment to patients, for what had been a neglected and underserved patient population. Ruxolitinib cream may improve the quality of life of patients with vitiligo by helping them achieve repigmentation. It has a good safety profile that allows patients to use it for a long time, which is not the case with TCS or TCI. Additionally, ruxolitinib may potentially help save costs associated with other treatment options, such as light therapy.

3j) Innovation

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

The first approved treatment for non-segmental vitiligo

Ruxolitinib cream is the first approved topical treatment that works to dampen the overactive immune system which is thought to cause vitiligo (4, 41).

An innovative mechanism of action

Ruxolitinib cream directly targets the process by which vitiligo develops (pathogenesis). It reduces the immune system's activity against the cells that produce melanin, allowing the skin to produce pigment and regain its normal colour (5).

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
No equality issues are foreseen in terms of providing ruxolitinib cream to eligible patients Ruxolitinib cream is intended for all patients from 12 years of age, as per the approval granted by the MHRA. Therefore, no equality issues are foreseen in terms of providing ruxolitinib cream to eligible patients. Access to light therapy (phototherapy) for patients with vitiligo varies across regions in the country. Currently in the NHS, dermatology waiting lists vary between 12-24 months for general dermatology clinics. In addition, once seen in secondary care, many patients with vitiligo are unable to start light therapy either due to long NHS waiting lists (over one year at some centres, following first assessment by a dermatologist) for this treatment option, and/or personal time constraints (i.e., the need to attend three times a week for 9-12 months). Furthermore, many dermatology departments offer light therapy to a small group of patients with vitiligo due to the prolonged course of treatment. As such, patients with other dermatological diseases (such as eczema or psoriasis) who usually require shorter courses are prioritised instead.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
• The British Association of Dermatologists (BAD) patient information leaflet: https://www.bad.org.uk/pils/vitiligo/ • Changing Faces: https://www.changingfaces.org.uk/advice-guidance/condition-specific-information/vitiligo/ • Vitiligo Society: https://vitiligosociety.org/ • NHS – vitiligo: https://www.nhs.uk/conditions/vitiligo/ Further information on NICE and the role of patients: • Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE • NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE • EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/

- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

- **Autoimmune:** A condition in which the body's immune system mistakes its own healthy tissues as foreign and attacks them.
- **CDLQI:** The children dermatology life quality index is a questionnaire designed to measure the impact of skin disease on the lives of children.
- **Chronic condition:** An illness persisting over a long time or constantly recurring
- **Depigmentation:** The loss of colour (pigment) from the skin.
- **DLQI:** The dermatology life quality index is a questionnaire used to measure the impact of skin disease on the quality of life of an affected person.
- **EQ-5D:** A standardised measure of health-related quality of life that assesses health status in terms of five dimensions of health. It is considered a 'generic' questionnaire because these dimensions are not specific to any one patient group or health condition.
- **F-VASI:** Facial vitiligo area scoring index is a reliable tool for assessing repigmentation on the patient's face.
- **F-VASI50:** 50% improvement in F-VASI
- **F-VASI75:** 75% improvement in F-VASI
- **F-VASI90:** 90% improvement in F-VASI
- .
- **Melanin:** A substance present in the skin that produces pigment (colour).
- **Non segmental vitiligo:** The most common type of vitiligo, accounting for 80% of patients with vitiligo. When a person has non-segmental vitiligo, patches tend to appear on both sides of the body like both hands or both knees.
- **Off-label use:** The use of pharmaceutical drugs for an unlicensed (unapproved) indication.
- **Segmental vitiligo:** A type of vitiligo that causes the skin to lose colour on one side or part of the body.
- **TRuE-V1:** Topical ruxolitinib evaluation in vitiligo study 1 is a phase 3 clinical study that evaluated the efficacy and safety of ruxolitinib cream in patients aged 12 years or older with NSV for whom total body involved vitiligo area did not exceed 10% body surface area.
- **TRuE-V2:** Topical ruxolitinib evaluation in vitiligo study 2 is a phase 3 clinical study that evaluated the efficacy and safety of ruxolitinib cream in patients aged 12 years or older with NSV for whom total body involved vitiligo area did not exceed 10% body surface area.
- **TRuE-V LTE:** Withdrawal and treatment extension study that assessed the long-term efficacy and safety of ruxolitinib cream
- **T-VASI:** Total body vitiligo area scoring index is a reliable tool for assessing repigmentation on the patient's body.
- **T-VASI50:** 50% improvement in T-VASI
- **T-VASI75:** 75% improvement in T-VASI

- **VitiQoL:** The vitiligo specific health related quality of life instrument is a questionnaire that assesses the burden of vitiligo on the quality of life of affected patients.
- **VNS:** a patient-reported measure that assesses how 'noticeable' vitiligo patches are after treatment.
- **Wood's lamp:** An ultraviolet (UV) lamp that doctors can use to examine the skin in more detail.

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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]

Clarification questions

September, 2023

File name	Version	Contains confidential information	Date
ID3998 ruxolitinib clarification letter to PM for company [CON]	1	Yes	13/09/2023

Section A: Clarification on effectiveness data

Analysis population and indication

A1. PRIORITY: In Table 2 of the company's submission, the licensed indication for ruxolitinib is described as: *"…* [non-segmental vitiligo] *with facial involvement in adults and adolescents from 12 years of age"*. However, the inclusion criteria for TRuE-V1 and TRuE-V2 explains that eligible patients must have non-segmental vitiligo *"with depigmented areas covering 10% or less of total body-surface area, including at least 0.5% of body-surface area on the face and at least 3% of body-surface area on non-facial areas."*

- **Please can the company clarify the definition of 'facial involvement' with respect to the generalisability of the licensed and trial populations?**

- **Please can the company clarify if there is a rationale related to the efficacy or safety of ruxolitinib that indicates treatment should be restricted to those with 'facial involvement'?**

The definitions of 'facial involvement' are the same between the licensed and trial populations. The lower F-BSA limit of 0.5% was selected as the most reasonable lower limit to be able to identify 'facial involvement' and to detect a change after treatment. The lower limit of 3% BSA on non-facial areas was based on the recommendation of investigator-initiated research (IIR) informing the Phase II protocol development (Study INCB 18424-211; see also response to A15 and the respective study CSR submitted together with the responses to the clarification questions) (1). This approach was deemed reasonable and aligned with anticipated clinical practice given a population that would receive JAK inhibitor treatment.

While there is no pharmacological or toxicological rationale for restricting treatment with ruxolitinib cream to patients with 'facial involvement', the clinical evidence supporting ruxolitinib cream in non-segmental vitiligo (NSV) is based on pivotal trials which featured an inclusion criterion of ≥0.5% F-BSA (2, 3), and the marketing authorisation for ruxolitinib cream limits its use to patients with NSV with facial involvement (4).

The company wish to point out that there is no generally accepted clinical definition of disease severity as exists for other dermatologic conditions. Extent of BSA affected by depigmentation is one consideration, but other clinical criteria, including anatomic location, visibility of lesions, the number of active lesions, and skin phototype, as well as subjective perception of disease contribute to the impact of vitiligo. In a recent study by van Geel et al. (2021) (5), participants ranked location (i.e., lesions in visible or sensitive areas) followed by disease extent and disease impact as the most important factors in the context of severity perception. Furthermore, involvement of exposed skin, such as the face and hands, can have a major impact on self-esteem, leading to an increased psychological burden and decreased quality of life (6). In a recently published study reporting the outcomes of workshops with patients with vitiligo, repigmentation of the face, hands and neck was recommended as a target for treatment (7-9).

The efficacy of ruxolitinib cream in non-facial areas is demonstrated in the T-VASI outcomes reported in the dossier and respective CSRs.

A2. PRIORITY. Throughout the appraisal, the company submission distinguishes between the trial population and the previously treated subgroup.

- **Please explain why a full set of results is not provided for the previously treated subgroup, if data from this subgroup are the most probative for the model.**
- **Please provide results for relevant outcomes pooled over prior therapies, as results in Table 20 are stratified by prior therapy when this is apparently irrelevant for the economic model.**

The company submission presents full results of efficacy and safety analyses conducted on the ITT and safety populations, respectively, and supplements these with results from post hoc analyses for the most salient outcomes pertaining to the cost-effectiveness analysis in the anticipated positioning for ruxolitinib cream.

The company have provided estimates of effect for efficacy endpoints by prior treatment status and imputation method together with the responses to these clarification questions.

Trial analysis

A3. Please provide estimates of effect at 24 and 52 weeks for all relevant outcomes using the range of imputation methods described.

Please refer to the CSRs for TRuE-V1 and TRuE-V2 (provided to NICE on the 11th August 2023) (10, 11), which report estimates of effects based on multiple imputation (main analysis) and on NRI. The LOCF imputation method was only carried out for the primary endpoint of TRuE-V1 and TRuE-V2 as an additional sensitivity analysis (see also responses to A2 and A8).

A4. Please provide additional detail and rationale relating to the pooling of studies.

Since TRuE-V1 and TRuE-V2 clinical trials have identical designs with the same primary and key secondary endpoints for the same population (2, 3, 10-12), the pooled efficacy analysis was conducted based on these two studies in the FAS (12). Details on the statistical analysis are provided in the statistical analysis plan of the pooled studies (please refer to the statistical analysis plan provided with these responses) (13). Analyses of the efficacy data for the pooled Phase 3 population are intended to support the results of the individual Phase 3 studies and provide a larger dataset for evaluating the treatment effect of ruxolitinib cream (12). Individual study results were consistent, details of which are provided in the respective CSRs (10, 11). Heterogeneity tests of the primary endpoint (F-VASI75 at week 24) from both studies yielded a p-value of 0.4835, confirming homogeneity.

A5. Please provide additional detail as to how multiple imputation was carried out, including the functional form used, any grouping variables, and how convergence was ascertained.

All multiple imputation (MI) analyses followed the universal algorithm for the primary endpoint (F-VASI 75 at week 24): a fully conditional specification (FCS) method (14) that assumes the existence of a joint distribution for all variables was used to impute F-VASI scores. A regression model including treatment group, stratification factors, and baseline using post baseline F-VASI scores up to Week 24 as outcomes was specified for the FCS method. After the missing values were imputed, the binary variables were derived based on the definition. The seed was 18424306 for TRuE-V1

and 18424307 for TRuE-V2, and the imputation was repeated 30 times to generate corresponding complete data sets to reflect the uncertainty around the true value. Exact logistic regression was applied to each imputed dataset, and then the results were combined for the inference. In each FCS resampling, a low number of iterations appears to be sufficient. Brand (1999) (15), and Van Buuren, Boshuizen and Knook (1999) (16) set the number of iterations quite low, usually somewhere between 5 to 20 iterations. In our analyses, the iteration number was set as 30 and this limit ensured convergence in all MI analyses.

A6. Please provide tests of proportional hazards for all time-to-event outcomes and summarise differences between curves using log-rank tests.

The company have provided log cumulative hazard plots and Schoenfeld residual plots for all time-to-event outcomes in Study TRuE-V LTE together with the responses to the clarification questions (please refer to the document titled 'A6. Log cumulative hazard curves and Schoenfeld residual plots'). Neither visual inspection of the log cumulative hazard plots and Schoenfeld residual plots nor p-values suggest that the proportional hazards assumption is violated. No time-to-event outcomes were assessed in the pivotal trials, TRuE-V1 and TRuE-V2 (2, 3).

Trial conduct

A7. A number of patients were excluded from Site 710.

- **Please clarify how these patients were identified and from which studies (including the long-term extension) these patients were removed.**
- **Please clarify how these exclusions were addressed in risk of bias assessment.**

The company wish to note that patients were not excluded from site 710, but that data from participants at site 710 (n = 13) of the TRuE-V2 study were removed from all efficacy analyses done on the ITT population for the final CSR owing to non-compliance with the protocol and concerns with the data quality. Data from participants at site 710 were included in all safety analyses (safety population and TE evaluable population) because all participants at site 710 applied the study drug at least once. As detailed in the TRuE-V LTE study disposition in document B (Figure 8), data from

2 patients were excluded from TRuE-V LTE Cohort A and from 1 patient from TRuE-V LTE Cohort B (17).

Data from TRuE-V1 and TRuE-V2 included 661 patients up to week 52, excluding those 13 patients from site 710 where major protocol violations were observed, as described above. A sensitivity analysis using the FAS and FAS without Site 710 was performed for the primary endpoint to evaluate if the change to the primary analysis population (from the FAS to the ITT population) impacted the study results. The impact of these 13 excluded subjects was marginal: at week 24, the re-calculated estimated F-VASI75 response rate without the 13 subjects from site 710 was not different from the estimated F-VAS75 previously reported including those subjects (30.7% versus 30.1% for ruxolitinib 1.5% BID, with response rate differences of 21.1% versus 19.3%). For the key secondary outcomes (F-VASI50, F-VASI90, T-VASI50 and the VNS score 4 or 5 at week 24), similar results were found, concluding that the data of these 13 subjects did not affect interpretation of the results (12).

A8. The company submission notes that Covid-19 affected the conduct of the trials. How was measurement of, for example, F-BSA undertaken in this context and was this compared to measurement undertaken in person?

BSA and VASI measurements were only conducted in person. If the subject missed the visit, the data was considered missing. Table 14 of document B presented sensitivity analysis around handling missing data and the proportion of patients achieving F-VASI75 at week 24 compared with vehicle were consistent. Patients did remove their masks for the assessment.

Missing values were originally planned to be handled using NRI. However, due to COVID-19 pandemic-associated impacts on clinical study participation, a decision was made before the database lock and unblinding to use MI instead (13). Multiple imputation, which provides an unbiased estimate of the parameters under the missing at random assumption (18), minimises potential bias from missing values and impact to study interpretation. Multiple imputation is considered a statistically powerful model that incorporates information on observed variables and improves the validity of the study and the ability to interpret treatment effects. Sensitivity analyses, including analyses using NRI (primary and key secondary endpoints) and last observation carried forward (primary endpoint only) to handle missing data and a tipping point

analysis (primary endpoint only), were performed to assess the robustness of the primary analysis results. The methods have been evaluated and considered valid following the specification of estimand attributes and sensitivity/supplemental analysis in the 2019 addendum to the ICH E9 (R1) guideline (19).

A9. In the TRuE-V1 and TRuE-V2 study publication by Rosmarin *et al.*, (2022), it states that *"Patients… were randomly assigned in a 2:1 ratio to apply 1.5% ruxolitinib cream or matching vehicle cream twice daily to all depigmented vitiligo lesions on the face and body identified at trial entry for 24 weeks"*. However, the SmPC states that the recommended dose is a thin layer of cream applied twice daily to the depigmented skin areas up to a maximum of 10% of body surface area (BSA). Please can the company clarify if there are any differences between the application guidance given to participants of the TRuE V1/TRuE V2 studies and per the SmPC?

There is no difference between the application guidance given to participants in the pivotal studies and the SmPC (2-4). Patients included in TRuE-V1 and TRuE-V2 had an affected BSA of 3.5-10% and applied the cream twice daily to all depigmented lesions (i.e., a maximum of 10% BSA as the patients recruited in the trial do not have more) (2, 3). Treatment up to 10% BSA in the pivotal trials was chosen as it is considered most appropriate for long-term, continuous treatment of vitiligo and based on the consensus guidelines regarding topical treatment rather than a safety concern to larger BSA (i.e., phase II trial had recruited patients with higher BSA); applying a topical treatment BID to an area greater than 10% BSA becomes difficult and impractical for most patients.

A10. Please clarify how treatment restart (for example, after relapse) was considered in the pivotal trials, or else where there is clinical evidence to support this administration strategy.

Treatment restart was not considered in the pivotal trials (i.e., TRuE-V1 and TRuE-V2) (2, 3). Guidelines for the interruption and restarting of study drug are provided in section 6.5 of the study protocol for TRuE-V LTE as well as per the design of the trial (responder F-VASI90 Cohort A participants continuing ruxolitinib cream or receiving vehicle) (20). For participants in Cohort A (i.e., participants with a ≥ F-VASI90 response at week 52 of the parent studies), if there was a loss of clinically meaningful

response on the face (i.e., < F-VASI75) at any time, the participants received open-label ruxolitinib cream 1.5% BID until completing the study (i.e., Week 104 or EOT) (20).

Clinician feedback suggests that retreatment is a clinically plausible option in patients who previously responded to treatment (≥25% repigmentation) but subsequently relapsed (see 'Summary of clinical validation') (21).

A11. Please can you clarify what background treatments were permitted and received in each arm during the clinical trials of ruxolitinib?

The treatment(s)/vaccination(s)/device(s) allowed or disallowed before, during, and/or after study treatment, including any exceptions to these requirements, are described in Sections 6.6 and 6.7 of the Protocols (provided together with the responses to the clarification questions) (2, 3, 20).

In TRuE-V1, concomitant medications were taken by 74.8% of participants during the DB period (please refer to Table 1.4.3.1 in the CSR) (10). By WHO drug class, medications used by ≥ 5% of participants included thyroid hormones (19.1%), propionic acid derivatives (14.8%), multivitamins (plain; 10.3%), 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors (8.2%), vitamin D and analogues (7.9%), anilides as well as progestogens and estrogens (fixed combinations; 7.3% each), angiotensin-converting enzyme inhibitors (plain; 6.7%), and other antihistamines for systemic use and piperazine derivatives (5.5% each). The most frequently used (≥ 3.5%) concomitant medications by WHO drug term were ibuprofen (10.9%), levothyroxine sodium and multivitamins (plain; 10.3% each), levothyroxine (7.6%), paracetamol (5.2%), fish oil and vitamin D NOS (4.2% each), lisinopril and metformin (3.9% each), and acetylsalicylic acid and vitamin B12 NOS (3.6% each). The most frequently used medications during the DB period were similar between the treatment groups and were generally consistent with those used prior to study entry (please refer to Table 1.4.2 in the CSR) (10).

In TRuE-V2, concomitant medications were taken by 71.7% of participants during the DB period (please refer to Table 1.4.3.1 in the CSR) (11). By WHO drug class, medications used by ≥ 5% of participants included thyroid hormones (14.6%); anilides (13.1%); propionic acid derivatives (9.9%); vitamin D and analogues (7.9%); 3-

hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors (6.4%); other antihistamines for systemic use and progestogens and estrogens, fixed combinations (6.1% each); and selective beta-2-adrenoreceptor agonists (5.2%). The most frequently used (≥ 3.5%) concomitant medications by WHO drug term were paracetamol (9.6%), levothyroxine sodium (7.9%), ibuprofen (7.6%), levothyroxine (6.4%), colecalciferol (4.4%), salbutamol (4.1%), ascorbic acid and vitamin D NOS (3.5% each). The most frequently used medications during the DB period were similar between the treatment groups and were generally consistent with those used prior to study entry (see Table 1.4.2 in the CSR) (11). Concomitant medications were taken by 134 participants (45.1%) during the TE period (please refer to Table 1.4.3.2 in the CSR) (11). By WHO drug class, medications used by ≥ 5% of participants included other viral vaccines (18.5%), anilides (8.4%), and propionic acid derivatives (7.1%). The most frequently used (≥ 3.5%) concomitant medications by WHO drug term were COVID-19 vaccine (18.5%), paracetamol (7.4%), and ibuprofen (5.1%) (11).

In TRuE-V LTE, in Cohort A, concomitant medications were taken by 81.0% of participants (see Table 1.4.3.2 in the CSR) (17). By WHO drug class, medications used by ≥ 10% of participants included other viral vaccines (30.2%); thyroid hormones and anilides (14.7% each); HMG-CoA reductase inhibitors (13.8%); propionic acid derivatives (11.2%); and progestogens and estrogens, fixed combinations (10.3%). The most frequently used concomitant medications by WHO drug term were tozinameran (21.6%) and paracetamol (12.9%). Other concomitant medications used by ≥ 5% of participants included elasomeran, ethinyl estradiol/levonorgestrel, ibuprofen and vitamins NOS, levothyroxine, levothyroxine sodium, salbutamol, and vitamin B12 NOS (17). The most frequently used medications were similar between the vehicle cream and ruxolitinib 1.5% cream BID treatment groups and were generally consistent with those used prior to study entry (please refer to Table 1.4.2.2 in the CSR) (17).

In Cohort B, concomitant medications were taken by 82.2% of participants (please refer to Table 1.4.3.1 in the CSR) (17). By WHO drug class, medications used by ≥ 10% of participants included other viral vaccines (28.7%); thyroid hormones and anilides (19.0% each); propionic acid derivatives (17.8%); and vitamin D and analogues (12.6%). The most frequently used concomitant medications by WHO drug

term were tozinameran (18.4%), paracetamol (14.6%), ibuprofen (14.0%), and levothyroxine sodium (10.2%). Other medications used by ≥ 5% of participants included ascorbic acid, colecalciferol and vitamins NOS, elasomeran, levothyroxine, metformin, and vitamin D NOS (17). The most frequently used medications were similar between participants initially randomised to vehicle cream in the parent study and those initially randomised to ruxolitinib 1.5% cream and were generally consistent with those used prior to study entry (please refer to Table 1.4.2.1 in the CSR) (17).

Of note, the Phase III study Protocols allowed concomitant use of emollients and sunscreen and included the following guidance on application in relation to topical ruxolitinib cream application (please refer to TRuE-V1 CSR Appendix 16.1.1 and TRuE-V2 CSR Appendix 16.1.1) (10, 11):

- *Emollients and mineral-based sunscreen with SPF of at least 30 were permitted but were not to be used within 2 hours after study drug application [to allow for adequate absorption of ruxolitinib cream]. Study drug was not to be applied over sunscreen; sunscreen must have been carefully removed from the to-be-treated skin before applying the study drug.*

Investigators and site staff were instructed to use their best clinical judgement with these recommendations and adhere to the guidelines as closely as possible.

A12. Please comment on the number of screening failures across TRuE-V1 and TRuE-V2 (Document B, Figure 6), providing details of the reasons behind screening failures and interpretating any implications for inference of results from the randomised samples.

Screening failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to study treatment (protocols of TRuE-V1 and TRuE-V2 studies) (2, 3). The eCRF completion guidelines tell investigator to choose screen failure if the participant has not met all inclusion/exclusion criteria, however, the specific criteria not met during screening were not collected and thus no comment can be made on the reasons of screening failure.

Indirect treatment comparison

A13. The company investigated the feasibility of undertaking an indirect treatment comparison, but it appears this was principally in respect of topical calcineurin inhibitors and topical corticosteroids. However, according to the company's proposed positioning, the optimal comparators are more likely to be treatments used in the second line setting, such as betamethasone with NB-UVB or NB-UVB with or without topical corticosteroid or calcineurin inhibitors. Please clarify the feasibility of indirect treatment comparisons vs second-line comparators, and if feasible, provide estimates of relative effectiveness.

As highlighted in Table 12 in Appendix D, the ITC feasibility assessment included topical or oral corticosteroids, topical or oral calcineurin inhibitors, phototherapy, laser therapy, topical vitamin D analogues and combinations of phototherapy with TCI or TCS. Section 1.2 in Appendix D provides details of the feasibility assessment, which explored data availability, risk of bias as well as between-study heterogeneity in terms of eligibility criteria, study outcomes, and patient demographic and disease characteristics across all included studies investigating the above treatments. The assessment of the indirect treatment comparisons being infeasible is therefore not limited to comparisons with TCS or TCI, but also to NB-UVB (note that oral betamethasone is not an appropriate comparator as the BAD guidelines explicitly recommend systemic therapy only for rapidly progressive disease (22), whereas the vast majority of patients in TRuE-V1 and TRuE-V2 had stable disease (10, 11); conversely, the guidelines contain no recommendation for use of topical therapy in rapidly progressive disease) (22). Additionally, there is insufficient network connectivity as evinced in the appended report (please refer to the document titled 'Ruxolitinib cream ITC feasibility report').

A14. The company's SLR identified a number of studies that evaluated alternative treatments for non-segmental vitiligo. On the basis of a feasibility assessment, the company concluded that an ITC to compare ruxolitinib with currently used treatments was not feasible and study-level characteristics (as used to inform the feasibility assessment) were provided in Appendix D of the submission. However, the results from these studies and a narrative synthesis

of the data were not provided. As stated in the NICE methods manual for technology appraisal, a comprehensive evidence base is necessary for appraisal, including quantification of the effect of the technology *and* its scoped comparators. This is the case even where ITC is ultimately not appropriate due to data limitations.

- **Please can the company provide tabulated clinical effectiveness data for all scoped outcomes from studies included in its SLR. If narrative synthesis was performed by the company as part of this review, please also provide this report. These data will allow the EAG to appraise the clinical effectiveness of ruxolitinib within the context of the current treatment pathway.**

The company have provided tabulated clinical effectiveness data from studies included in the SLR the responses to the clarification questions. The file is titled 'Vitiligo Clinical SLR Data Grid 27042023'. Due to the infeasibility of robust evidence synthesis for reasons detailed in section 1.2 of Appendix D, no narrative synthesis was performed.

Phase II trial of ruxolitinib

A15. A phase II trial of ruxolitinib was identified in the company's SLR but full details of this study and its findings are not reported in the company submission. Can the company please provide this information or else provide a clear rationale for its exclusion from the appraisal?

The CSR for the Phase II study is provided with the responses to the clarification questions. Study INCB 18424-211 is a Phase II, randomized, double blind, vehicle-controlled dose range finding study in adult participants (aged 18-75 years) with vitiligo to assess the efficacy and safety of ruxolitinib cream (1, 23). The Phase II dose range-finding study is supportive and was the basis for the selection of the 1.5% BID regimen, the thresholds for primary and key secondary endpoints using the VASI, and the treatment duration during the double-blind period in the Phase III studies (23).

Section B: Clarification on cost-effectiveness data

Key model assumptions and use of clinical effectiveness data

B1. PRIORITY. Given the comparator arm of TRuE-V1 and TRuE-V2 studies is vehicle cream (which in isolation should have no effect on re-pigmentation), please can the company provide further justification for its position that this is an (the) appropriate comparator for this appraisal? That is, explain a situation in which patients in NHS England practice, after initial topical treatments, would next be offered vehicle cream, before, as the company's model assumes, the potential for receiving NB-UVB treatment is introduced.

In patients with vitiligo whose disease has not responded to initial treatment with TCS or TCI, the current BAD guidelines recommend offering either NB-UVB +/- TCS or TCI, or considering oral betamethasone specifically for rapidly progressive disease (22). Neither of these options are appropriate comparators for the appraisal of ruxolitinib cream for the following reasons:

A retrospective cohort study amongst vitiligo patients in the UK found that among the prevalent cohort of 44,910 patients in 2019, 85.0% of patients were not on vitiligo-related treatment. In the first year after diagnosis, 60.8% of patients did not receive any vitiligo-related treatment (e.g., topical steroids, topical calcineurin inhibitors, oral steroids, phototherapy), increasing to ≥82.0% from the second year onward (24). This finding is indicative of the vast majority of prevalent patients, including those with prior failure with TCS or TCI, not proceeding to another line of off-label therapy. In the first year, patients were recorded as having been prescribed topical corticosteroids (29.1%), topical calcineurin inhibitors (11.8%), and oral corticosteroids (4.2%). From the second year onward, the percentage of patients prescribed oral corticosteroids remained stable, while prescription of topical corticosteroids and calcineurin inhibitors declined to 11.4% and 3.9% in the second year, respectively, remaining low thereafter (24).

In addition, the anticipated positioning of ruxolitinib cream in the treatment pathway is as a step change option between first and second line for adults and adolescents from 12 years of age with NSV with facial involvement. Given the availability of generic TCS and TCI, ruxolitinib cream is not anticipated to be cost-effective in the full population.

Therefore, this positioning is considered most appropriate since introduction of a topical treatment after failure of initial topical treatment but prior to phototherapy is less burdensome for patients with vitiligo and less of a strain on NHS resources. Furthermore, there remains a lack of equitable access to phototherapy, which is further compounded by other competing chronic inflammatory skin disease indications for phototherapy such as psoriasis and atopic dermatitis, resulting in long wait times and variability in receiving this treatment option across the UK. Finally, and more fundamentally, clinicians generally recommend that phototherapy is prioritised for patients with large BSA (i.e., >10%) affected (21, 25).

Oral betamethasone is not an appropriate comparator as it is explicitly recommended only for rapidly progressive disease (22), whereas the vast majority of patients in TRuE-V1 and TRuE-V2 had stable disease (10, 11).

a. In the absence of convincing justification, please respecify the cost-effectiveness comparison at an appropriate point in the treatment pathway, with appropriate comparators. Provide a revised version of the cost-effectiveness model incorporating these changes and other updates requested in this document. To allow EAG verification of this revised model, please retain the functionality for the model user to easily revert to the originally submitted results. Provide supportive documentation both explaining and justifying the company's revised cost-effectiveness approach and explaining how the EAG can revert to originally submitted results.

Please see the response to B1 which justifies vehicle comparator and positioning. Furthermore, as described in A14, an ITC was not feasible and could not be incorporated within the cost-effectiveness model.

B2. PRIORITY. Table 22 of Document B of the company's submission is presented as summarising data availability for outcomes of interest in studies with vitiligo, and used as justification for a conclusion of incomparable outcome measures across studies: "*Notably, F-VASI (the primary endpoint in the TRuE-V studies) and T-VASI were not reported in any study, other than TRuE-V1, TRuE-V2, and the Phase 2 clinical trial of ruxolitinib cream for the treatment of vitiligo (see Table 22)*" (Document B, Page 84). However, in the company's approach to utility value estimation, the company explicitly assume

F-VASI, VASI and re-pigmentation score data are interchangeable. At least one of the studies in Table 22 reports re-pigmentation score; Thomas (2021), which the EAG read as the Br J Dermatol publication of HI-Light Vitiligo Trial data, citation 110 in Document B. Re-pigmentation data from the HI-Light trial inform the company's approach to utility data estimation. Yet, Table 22 presents this study as not presenting useful efficacy data.

a. Please provide a revised version of Table 22, in which (i) the outcome measures used in each study are faithfully reported and (ii) the treatments in each arm of each study are summarised.

Thank you for the question. Table 22 in Document B provides a faithful overview of the data availability for outcomes of interest in studies with vitiligo. It is correct that Thomas et al., 2021 (26) present the results of the HI-Light trial, including percentage repigmentation. A comparison of outcomes between the HI-Light trial (Thomas et al. 2021) (26) and the TRuE-V studies was not deemed feasible as the primary endpoint of the latter was F-VASI75 (2, 3), and the two measures therefore are not identical *clinical* measures. The company do not argue that F-VASI, VASI and RPS (with RPS being used in the utility analysis) are interchangeable – note that the Vitiligo Area Scoring Index integrates the body-surface area with a depigmentation score and as such takes into account lesion integrity as opposed to margins only – but merely that RPS is a reasonable proxy for F-VASI specifically on impact of quality of life to enable utility data estimation.

b. In a revised cost-effectiveness model and supported by written documentation of approach to indirect comparison and any additional modelling assumptions, provide cost-effectiveness comparisons to those treatments listed as second-line treatments in the BAD guidelines referenced in the company's submission. That is,

- **NB-UVB with or without topical corticosteroid or calcineurin inhibitors**
- **For patients with rapidly progressing disease, oral betamethasone in delayed combination with NB-UVB**

As explained in responses to B1 and A13, neither NB-UVB +/- TCS or TCI nor oral bethametasone are appropriate comparators for the appraisal of ruxolitinib cream in the anticipated positioning as step change option between first line and second line.

B3. Given the results in Figure 18 of Document B, and in particular the result for adolescent patients, could the company please comment on its decision to assume the cost-effectiveness model cohort is homogeneous with respect to age, without exploration of costs and health outcomes separately for adolescent and adult subpopulations?

Ad hoc subgroup analyses were performed on pooled data from the confirmatory Phase 3 studies for the primary and key secondary endpoints to assess the consistency of the ruxolitinib 1.5% cream treatment effect between adolescents (12 to < 18 years) and adults (≥ 18 years). The results of these subgroup analyses demonstrate a treatment effect of ruxolitinib 1.5% cream (i.e., higher response rates for the ruxolitinib 1.5% cream treatment group compared with the vehicle cream treatment group) on each of the endpoints for adolescents and adults, with similar response rates and percent change in F-BSA for the age groups (see **Table 1**). Response rates and the percent change in F-BSA for these efficacy variables during the 28-week treatment extension period demonstrate continued improvement in repigmentation of vitiligo beyond Week 24 for adolescents and adults who were initially randomized to the ruxolitinib 1.5% cream treatment group.

Table 1: Summary of Results for the Primary and Key Secondary Endpoints (ITT Population)

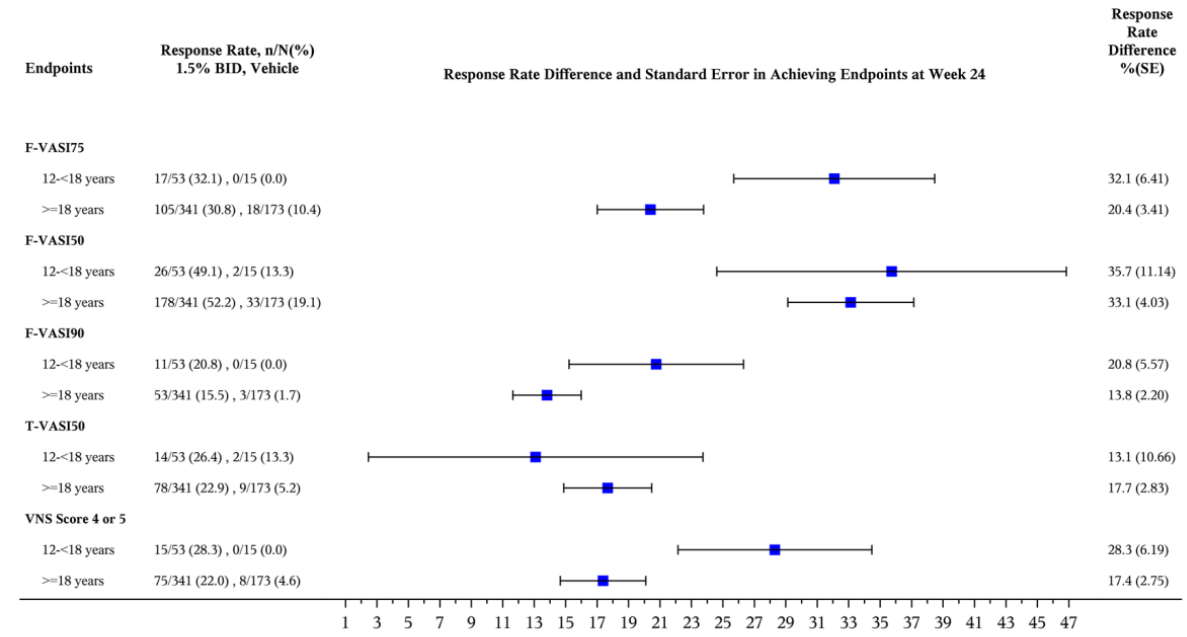
Endpoint	Adolescents (12 to < 18 Years)		Adults (≥ 18 Years)	
	Vehicle Cream BID (N = 17)	Ruxolitinib 1.5% Cream BID (N = 55)	Vehicle Cream BID (N = 201)	Ruxolitinib 1.5% Cream BID (N = 388)
F-VASI75				
Week 24	0/15 (0)	17/53 (32.1)	18/173 (10.4)	105/341 (30.8)
Week 52	2/14 (14.3)	24/50 (48.0)	44/149 (29.5)	152/300 (50.7)
F-VASI50				
Week 24	2/15 (13.3)	26/53 (49.1)	33/173 (19.1)	178/341 (52.2)
Week 52	5/14 (35.7)	35/50 (70.0)	81/149 (54.4)	226/300 (75.3)
F-VASI90				
Week 24	0/15 (0)	11/53 (20.8)	3/173 (1.7)	53/341 (15.5)
Week 52	1/14 (7.1)	12/50 (24.0)	22/149 (14.8)	94/300 (31.3)
T-VASI50				
Week 24	2/15 (13.3)	14/53 (26.4)	9/173 (5.2)	78/341 (22.9)
Week 52	3/14 (21.4)	30/50 (60.0)	41/149 (27.5)	149/300 (49.7)
VNS of 4 or 5				
Week 24	0/15 (0)	15/53 (28.3)	8/173 (4.6)	75/341 (22.0)
Week 52	2/14 (14.3)	28/50 (56.0)	25/149 (16.8)	99/300 (33.0)
F-BSA				
Week 24	4.53 (42.312)	−27.75 (36.881)	−10.41 (25.258)	−28.62 (35.410)
Week 52	−21.49 (30.935)	−41.93 (53.118)	−28.56 (39.877)	−43.56 (37.434)

Note: All participants applied ruxolitinib cream 1.5% cream BID after Week 24.
Note: Results for F-VASI75, F-VASI50, F-VASI90, T-VASI50, and VNS of 4 or 5 are reported as number of participants who responded/number of participants with non-missing values (%).
Note: Results for F-BSA are reported as LSM percentage change from baseline (STD).

Subgroup analyses of the proportion of participants in the pooled Phase 3 population achieving F-VASI75 at Week 24 were performed to assess the consistency of the ruxolitinib 1.5% cream BID treatment effect based on intrinsic (age group, sex, race, skin type, and baseline F-BSA score) and extrinsic (geographic region) factors.

A forest plot for the differences between the ruxolitinib 1.5% cream BID and vehicle cream treatment groups for the primary and secondary endpoints by age category is provided in **Figure 1**. Participants in the ruxolitinib 1.5% cream BID treatment group consistently had a better response than those in the vehicle cream treatment group regardless of subgroup, although there was variability in the magnitude of response within each subgroup. It should be noted that the sample size in the adolescent age group (i.e., 12-<18 years) was relatively small (n=53), therefore these data should be interpreted with caution.

Figure 1: Forest plot of response rate differences for the primary and secondary endpoints by age category, pooled data from TRuE-V1 and TRuE-V2



Note: Data from participants enrolled at Site 710 in Study INCB 18424-307 were excluded.

Source: EPAR public assessment report, Figure 28 (12).

As planned, at least 10% of participants in each study were adolescents.

As given by the 'summary of clinical validation', it was stated by Clinical Expert 2 that the treatment strategy for adolescents and adults are very similar with the clinical expert expecting the tariff for adolescents to be at a higher value. Therefore, the model applies a conservative approach of equal cost for both the adolescent and adult population (21).

B4. PRIORITY. Throughout Document B, the company cites discussions with experts that informed or validated assumptions in the company's approach (citations 122 ["Incyte. Summary of model validation discussions. 2023"] and 123 ["Incyte. Summary of clinical validation discussions. 2023."]). As part of a full reference pack for all company references, please provide sufficient details of these meetings, including but not limited to: attendees, agenda, any materials shared in advance and during the meetings, any minutes taken.

Please ensure that the approach to eliciting psychological support medical resource use is clear.

The company have provided the summary of clinical validation discussions and the summary of model validation discussions with the responses to the clarification questions. The files are titled ‘Summary of economic validation V1’ and ‘Summary of clinical validation V1’ (21, 27).

B5. The company’s model includes a switch to change the timepoint of initial response from ‘week 24’ to ‘week 52’ (‘dropdown_timepoint’ in the submitted model file).

a. Please clarify if this is an exploratory analysis which should not be considered as part of this appraisal, or if this is an alternative proposed treatment strategy for ruxolitinib that should be considered as part of this appraisal?

The model base case considers a treatment strategy of 24 weeks of treatment before assessment of initial response in line with the double-blind period of the TRuE-V studies due to the reduced uncertainty on vehicle arm compared to a response assessment at 52 weeks. As described in the submission, an assessment of initial response at week 52 would require further assumptions to be made in the absence of comparative data. However, the results of the pivotal trials suggest that longer treatment with ruxolitinib cream is beneficial to the patient. The company would welcome the consideration of this alternative treatment strategy as part of this appraisal.

b. Similarly, please clarify if the alternative initial response definitions are also relevant to this appraisal (‘Drop Down 13’ in the submitted model file)?

The primary endpoint of the pivotal trials was defined as F-VASI75, thus this definition was used for the assessment of initial response in the model base case. In addition, F-VASI75 is considered as a minimal clinically important difference (MCID) for patients – based on patient interviews conducted by Incyte in Phase II/III clinical development for ruxolitinib cream (please refer to the file titled ‘Patient exit interviews_INCB18424-306307’) – and in the published literature (28). For these reasons the company would

like F-VASI75 to be considered the most relevant definition of initial response in this appraisal.

B6. In Section B.3.2. of the company's submission, the decision to include retreatment is justified on the basis of clinical opinion: *"It was also noted by the clinicians that in clinical practice, patients who had a loss of response (i.e., experienced depigmentation) after an initial response to therapy (i.e., experiencing regimentation) may be retreated to regain response (i.e., repigmentation levels returning to repigmentation noted in the previous stable state)"*. Given this advice, please could the company explain why one re-treatment course was captured within the model structure, rather than multiple re-treatment courses, for <u>both</u> treatment arms (i.e., ruxolitinib cream and vehicle cream)?

The modelling of re-treatment in the cost-effectiveness model is aligned with the TRuE-V LTE study (17, 20). The TRuE-V LTE study captured the response to re-treatment for participants who experienced relapse. That is, the time to regain repigmentation responses after restarting ruxolitinib cream in participants who relapsed. Importantly, in this extension study, participants were only retreated once, and following re-treatment only a small number of participants relapsed and therefore would be eligible for a second course of re-treatment, for which there is no available data. That is, 8 (14.5%) and 16 participants (28.6%) of those randomised to ruxolitinib 1.5% cream and vehicle cream, respectively, relapsed in the LTE phase (17). The model is faithful to the available data to ensure compatibility of the model structure to the trial data. Clinical experts confirmed that they would expect to retreat patients who relapse in practice (please refer to 'Summary of clinical validation') (21), however, whether patients are retreated and how many times they are re-treated is uncertain and may be impacted by multiple factors including patient choice. In the absence of data, modelling multiple retreatment courses was deemed likely to add substantial uncertainty to the model results.

B7. Please provide a sensitivity analysis that allows for re-treatment to be disabled in the model (where patients that relapse from the 'stable' health state move to the 'non-response' health state, without first being re-treated). If

feasible, please provide this scenario in a manner which allows for re-treatment to be permitted for a proportion of patients.

Thank you for the request to update the model with a switch for retreatment and for the proportion of patients being re-treated to be user-editable. The model has been updated accordingly and is provided together with the response to the clarification questions. **Table *2*** presents the deterministic results at PAS price.

Table 2. Deterministic summary results at PAS price with retreatment, prior therapy population

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)
Vehicle cream	0.038	[redacted]	[redacted]	-	-	-	-
Ruxolitinib cream	0.455	[redacted]	[redacted]	0.418	[redacted]	[redacted]	£19,355

In the retreatment scenario, it is assumed that 68% of patients who relapsed are retreated. This results in 1.87% of patients from the overall cohort being retreated with ruxolitinib cream. In the base case assuming that 100% of patients who relapsed are retreated, 2.74% of patients from the overall cohort are retreated with ruxolitinib cream.

B8. PRIORITY. In Table 33 of Document B of the company's submission, discontinuation within the initial and maintenance periods are presented using pooled results of TRuE-V1 and TRuE-V2.

a. Please provide TRuE-V1 and TRuE-V2 Kaplan-Meier time to treatment discontinuation data, stratified by study and treatment arm, for relevant TRuE-V1 and TRuE-V2 populations. Please provide these data within an .xls file.

The company have provided Kaplan-Meier for time-to-treatment discontinuation as an .xls file together with the responses to these clarification questions.

b. Using the output from a., please incorporate functionality into the revised model to allow time-to-treatment discontinuation to be accurately modelled. If deemed appropriate, please clarify any

adjustments made to these data before incorporation within the economic model (e.g., to align with company assumption of postponement of discontinuation events until week 24 for concordance with response assessment). Please also justify this discontinuation postponement assumption.

At the clarification call with the EAG on the 1st September 2023, it was agreed that the incorporation of time-to-treatment discontinuation (TTD) within the revised model was not required.

B9. Please provide scenarios using transitions estimated from alternative imputation methods (e.g., non-responder imputation). For example, where relevant, using the different imputation methods described in Table 11.

The company have provided deterministic results of scenario analyses using transitions estimated from alternative imputation methods together with the responses to the clarification questions. **Table 3**, **Table 4** and **Table 5** below present results for the observed cases, the observed cases and non-responder imputation (NRI), and the observed cases and last observation carried forward (LOCF) imputation, respectively.

The company notes that an inconsistency in the code for producing simple response (F-VASI only) inputs was identified while addressing this question. The clinical data analysed, which includes the initial and sustained response estimates and contributed to the derivation of the transition matrices, had inadvertently used a mix of LOCF and NRI methods for the F-VASI data of patients with missing measurements. Following rectification, analyses were re-run using the following F-VASI data:

- Observed cases only
- NRI measurements
- LOCF imputed measurements

Table 3. Deterministic summary results at PAS price with observed cases dataset, prior therapy population

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)
Vehicle cream	0.056	[redacted]	[redacted]	-	-	-	-
Ruxolitinib cream	0.540	[redacted]	[redacted]	0.485	[redacted]	[redacted]	£10,642

Table 4. Deterministic summary results at PAS price with observed cases dataset and non-responder imputation, prior therapy population

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)
Vehicle cream	0.041	[redacted]	[redacted]	-	-	-	-
Ruxolitinib cream	0.500	[redacted]	[redacted]	0.459	[redacted]	[redacted]	£11,378

Table 5. Deterministic summary results at PAS price with corrected observed cases dataset and last observation carried forward imputation, prior therapy population

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)
Vehicle cream	0.056	[redacted]	[redacted]	-	-	-	-
Ruxolitinib cream	0.540	[redacted]	[redacted]	0.485	[redacted]	[redacted]	£10,642

Cost and resource use and health-related quality of life inputs

B10. PRIORITY. In the company's model, no dosing details are provided beyond a pooled trial estimate of daily dose, reported to two decimal places.

To allow accurate estimation of expected treatment acquisition costs and further exploration of potential treatment acquisition costs, please provide:

a. (anonymised) patient-level BSA data from TRuE-V1 and TRuE-V2, stratified by trial and treatment arm

b. (anonymised) patient-level dosing data from TRuE-V1 and TRuE-V2, stratified by trial and treatment arm

c. In the company's model, the average daily dose of ruxolitinib is estimated based on pooled TRuE-V data for both arms. Please can the company provide summary statistics for daily dose for the ruxolitinib and vehicle cream arms separately?

a) The company has explored obtaining the data requested by the EAG. Unfortunately, this data was not previously anonymised. To ensure data privacy standards are maintained, the process to anonymise the clinical trial patient level data is likely to take 4-6 weeks as this is undertaken by an external vendor through an internal SOP. Provision of the data in line with these timelines is likely to take Incyte out of the prescribed appraisal process. Regrettably, the company is unable to meet the request of the EAG at this time.

b) Similar to a), regrettably the company is unable to meet the request of the EAG at this time.

c) Please see below for a short description and summary statistics for the daily dose of ruxolitinib cream from TRuE-V1 and TRuE-V2.

Study drug exposure during the double-blind period as well as cumulative exposure through Week 52 for participants who applied ruxolitinib 1.5% cream BID in TRuE-V1 is summarised in **Table 6**. Participants applied ruxolitinib 1.5% cream BID for a median of 168.00 days in the double-blind period. The median daily amount of ruxolitinib 1.5% cream BID applied during the double-blind period (4.17 g) and over the double blind plus treatment extension period (4.29 g) was similar.

Table 6. Summary of Study Drug Exposure for Participants Who Applied Ruxolitinib Cream (Safety Population) – TRuE-V1

Variable	Ruxolitinib 1.5% Cream BID	
	Exposure in Double Blind Period	**Cumulative Exposure in Double Blind and Treatment Extension Periods**
Duration of treatment	*During the DB period (days)*	*From Day 1 through Week 52 (days)*
n	221	[redacted]
Mean (STD)	159.97 (32.257)	[redacted]
Median	168.00	[redacted]
Min, max	1.0, 237.0	[redacted]
Average weight of study drug applied daily	*During the DB period (g)*	*From Day 1 through Week 52 (g)*
n	221	[redacted]
Mean (STD)	5.82 (16.587)	[redacted]
Median	4.17	[redacted]
Min, max	0.4, 237.1	[redacted]
Total weight of study drug applied	*During the DB period (g)*	*From Day 1 through Week 52 (g)*
n	221	[redacted]
Mean (STD)	691.12 (369.961)	[redacted]
Median	632.50	[redacted]
Min, max	61.0, 1434.6	[redacted]

Note: Duration of treatment was defined as the duration from the first application of study drug to the last application of study drug.
Note: Average weight of study drug applied daily (g) = total weight of study drug applied/(duration of treatment − interrupted days).
Source: CSR Table 3.1.1.3. and EPAR Table 20.

Study drug exposure during the double-blind period as well as cumulative exposure through Week 52 for participants who applied ruxolitinib 1.5% cream BID in TRuE-V2 is summarised in **Table 7**. Participants applied ruxolitinib 1.5% cream BID for a median of 168.00 days in the double-blind period. The median daily amount of ruxolitinib 1.5% cream applied during the double-blind period (3.96 g) and over the double blind plus treatment extension period (4.48 g) was similar.

Table 7. Summary of Study Drug Exposure for Participants Who Applied Ruxolitinib Cream (Safety Population) – TRuE-V2

Variable	Ruxolitinib 1.5% Cream BID	
	Exposure in Double Blind Period	**Cumulative Exposure in Double Blind and Treatment Extension Periods**
Duration of treatment	*During the DB period (days)*	*From Day 1 through Week 52 (days)*
n	228	[redacted]
Mean (STD)	157.93 (37.465)	[redacted]
Median	168.00	[redacted]
Min, max	1.0, 220.0	[redacted]
Average weight of study drug applied daily	*During the DB period (g)*	*From Day 1 through Week 52 (g)*
n	228	[redacted]
Mean (STD)	8.86 (31.385)	[redacted]
Median	3.96	[redacted]
Min, max	0.4, 237.0	[redacted]
Total weight of study drug applied	*During the DB period (g)*	*From Day 1 through Week 52 (g)*
n	228	[redacted]
Mean (STD)	674.23 (396.067)	[redacted]
Median	579.00	[redacted]
Min, max	11.2, 1442.7	[redacted]

Note: Duration of treatment was defined as the duration from the first application of study drug to the last application of study drug.
Note: Average weight of study drug applied daily (g) = total weight of study drug applied / (duration of treatment – interrupted days).
Source: Table 3.1.1.3. and EPAR table 20

Please see below for further detail on ruxolitinib cream and vehicle cream consumption from the pooled TRuE-V studies (**Table 8**; **Table 9**).

Table 8. Ruxolitinib cream and vehicle cream gram per day consumption data from pooled TRuE-V1 and V2

Gram per day	TRuE-V1 and V2 pooled
Median weight of study drug applied daily during the Double-Blind period	
Ruxolitinib 1.5% Cream BID	4.07 g
Vehicle Cream BID	3.81 g
Total (Rux cream + Vehicle)	4.03 g
Median weight of ruxolitinib cream applied daily from Day 1 through Week 52	
Ruxolitinib 1.5% Cream BID	4.37 g

Source: Data on file

Table 9. Ruxolitinib cream and vehicle cream dose per day per BSA consumption data from pooled TRuE-V1 and V2

Dose per day per BSA	TRuE-V1 and V2 pooled
Median dose per day per BSA during the Double-Blind period	
Ruxolitinib 1.5% Cream BID	0.59 g
Vehicle Cream BID	0.56 g
Total (Rux cream + Vehicle)	0.59 g
Median dose per day per BSA from Day 1 through Week 52	
Ruxolitinib 1.5% Cream BID	0.64 g

Source: Data on file

In a real-world setting, it is likely that the consumption of ruxolitinib cream would be lower. This is evidenced by the VALIANT study (29) which gives a median affected BSA (% of total body) of 3.78 compared to 7.70 from the TRuE-V studies (pooled TRuE-V; Table 8 presented in Document B). The median BSA population in TRuE-V1/2 studies are higher due to the inclusion criteria of 3.5-10% BSA and higher compliance observed in clinical trial vs real-life.

B11. In Table 40 of Document B of the company's submission, several drug costs are included (such as the costs of vitamin D supplement, camouflage, etc.). Please can the company provide further details regarding how these costs were identified (including, for example, screenshots from the BNF for which precise costs were identified), to allow EAG verification.

The sources for concomitant and BSC therapies included in Table 40 of the company's evidence submission are described in full in the cost inputs sheet of the cost-effectiveness model. The source includes the pack size and manufacturer, taken from the British National Formulary in July 2023. Items selected were those with the lowest NHS indicative price at the time of cost collection. The company notes that NHS indicative prices for vitamin D, tacrolimus and oral dexamethasone have since been updated. The BNF was last updated on 26th July 2023, whereas the period of company cost collection was earlier in July. The lowest NHS indicative prices as of September 2023 are listed in **Table 10** below.

Table 10. BNF sources for concomitant and BSC therapy costs

Therapy item	Pack size	Pack cost (Jul 2023)	Name & Manufacturer	Pack cost (Sep 2023)	Name & Manufacturer	Source
Vitamin D supplement	48000 IU	£1.99	Colecalciferol Vitamin D3 400 IU tablets (Prohealth Solutions Ltd)	£1.70	FSC Vitamin D3 400 IU tablets (Bee Health Ltd)	BNF (30)
Camouflage	30.00 g	£11.86	Dermacolor camouflage creme (Covermark classic foundation 15 ml) (Derma UK Ltd)	£11.86	Dermacolor camouflage creme (Covermark classic foundation 15 ml) (Derma UK Ltd)	BNF (30)
Fixing powder	60.00 g	£10.84	Dermacolor fixing powder (60 grams) (Kryolan UK Ltd)	£10.84	Dermacolor fixing powder (60 grams) (Kryolan UK Ltd)	BNF (30)
Tacrolimus	60.00 g	£31.64	Tacrolimus 0.1% ointment (Alliance Healthcare (Distribution) Ltd)	£30.50	Tacrolimus 0.1% ointment (Alliance Healthcare (Distribution) Ltd)	BNF (30)
Mometasone	100.00 g	£10.57	Mometasone 0.1% ointment (Viatris UK Healthcare Ltd)	£10.57	Mometasone 0.1% ointment (Viatris UK Healthcare Ltd)	BNF (30)
Oral dexamethasone	56.00 mg	£2.81	Dexamethasone 2 mg tablets (Alliance Healthcare (Distribution) Ltd)	£2.03	Dexamethasone 2 mg tablets (Alliance Healthcare (Distribution) Ltd)	BNF (30)

Please refer to the documents submitted with the responses to the clarification questions for screenshots from the BNF website.

Please also refer to the updated Appendix K for further details.

B12. In Section B.3.5.2 of the company's submission, the approach taken to inform medical resource use is described.

a. **Please can the company provide further detail regarding how the values that inform the company's model (presented in Table 41 of the company's submission) were estimated using a combination of information reported by Sach *et al.*, (2021) and the previous NICE appraisal TA621?**

The medical resource use was informed by Sach et al., 2021 (31) and TA681 (32). Sach et al., 2021 provide the following values in the publications (**Table 11***)* (31).

Table 11. Resource use items, Sach et al., 2021

Resource Item (Sach et al. 2021)		TCS mean use (± SD)	TCS mean use over 4 weeks	TCS mean costs (± SD)	Combination mean use (± SD)	Combination mean use over 4 weeks	Combination mean costs (± SD)
1	Dermatologist time (clinic + telephone)	4.00 (0.00)	0.409	546.00 (0.00)	4.00 (0.00)	0.409	546.00 (0.00)
2	Unscheduled clinic with dermatologist	0.02 (0.13)	0.002	2.24 (16.89)	0.10 (0.43)	0.010	13.30 (55.50)
3	Unscheduled telephone with dermatologist	0.02 (0.17)	0.002	1.73 (16.96)	0.05 (0.27)	0.005	5.14 (26.80)
4	Nurse time (clinic + telephone)	0.00 (0.00)	0.000	0.00 (0.00)	2.00 (0.00)	0.204	72.00 (0.00)
5	Unscheduled clinic with nurse	0.01 (0.11)	0.001	0.21 (1.93)	0.13 (0.51)	0.013	2.41 (9.53)
6	Unscheduled telephone with nurse	0.39 (0.87)	0.040	7.16 (16.30)	0.66 (1.29)	0.067	12.30 (23.90)
7	Primary care and community [number]	0.12 (0.44)	0.012	3.90 (15.20)	0.12 (0.55)	0.012	2.84 (14.10)
8	Secondary care [number]	0.48 (4.47)	0.049	11.10 (77.10)	0.20 (0.63)	0.020	8.52 (26.90)

The cost categories considered in TA681 (32) are as follows: dermatologist outpatient consultation (consultant led), dermatologist telephone appointment (consultant led), dermatologist nurse visit, GP consultation, hospitalisation, accident and emergency visit. Of note, hospitalisation was not included in the submitted model as clinical validation stated that vitiligo does not lead to hospitalisation (please refer to the 'summary of clinical validation' provided in the reference pack). Further, psychological support was not referenced in TA681 (32) (or Sach et al., 2021) (31) but was discussed by clinicians as forming part of the care package for patients due to the psychological impact of vitiligo on patients. The resource use frequencies for psychological support over a six-month period were provided by the two clinicians and a simple average of their values was estimated and then converted to the cycle-specific length of four weeks. The values provided by the clinicians and the associated calculations are provided in Appendix M. The costing categories in Sach et al., 2021 (31) were used to inform the TA681 categories as Sach et al is a relevant and recent vitiligo-based trial

whilst the evidence presented in TA681 (32) contributed to a positive reimbursement decision.

To generate the values for the resource use for the ‘initial’, ‘maintenance’ and ‘retreated’ health states, the TCS arm of the Sach et al., publication (31) was used but converted to a four-week resource use. For dermatologist outpatient consultation (consultant led), resource use 1 and 2 were combined; telephone-based appointment was taken as equivalent to 'unscheduled telephone consultation with dermatologist (resource use 3)’; ‘dermatologist nurse visit' is formed of the combination of resource use 4, 5 and 6; ‘GP consultation’ is taken as equivalent to ‘primary care and community’ (resource use 7); finally, ‘accident and emergency' is taken as half of the resource use listed for ‘secondary care’ (resource use 8). For the non-response state, the same resource use categories are used to generate the resource use values, however, the combination arm from Sach et al., 2021 (31) is used to inform these values. Resource use estimates for stable state were retrieved from the two clinicians due to lack of data from any published source, whereas for the stable retreated state the same estimates with those provided for the stable state were assumed.

The resource use, and corresponding cost, was validated by clinicians; please refer to the ‘summary of clinical validation’ for further detail.

Please refer to Appendix M for further detail.

b. In addition, please can the company confirm that the estimates of standard error (SE) are assumed to be 10% of the mean value for each resource use frequency?

The company can confirm that the estimates of standard error are assumed to be 10% of the mean value for each resource use frequency. This is considered a typical approach in the lack of uncertainty measures.

B13. Please can the company confirm that the following understanding of the approach to elicit utility values is correct:

- **EQ-5D data were not collected in TRuE-V1 and TRuE-V2, though data from other health-related quality of life measures were, including DLQI (not used in the model) and VitiQoL (used as described below)**

- **A published mapping algorithm by Begum *et al.*, (2023) provides a means of generating EQ-5D-3L (Hernandez et al cross-walked) utility values from RPS, VNS and VitiQoL data**

- **RPS is equivalent to change in VASI, as reported in Begum *et al.*, (2023). The company deem VASI to be a good proxy for F-VASI, such that change from baseline in F-VASI can be used in place of RPS, in a Begum *et al.*, (2023) RPS algorithm.**

- **Changes from baseline F-VASI from TRuE-V1 and TRuE-V2 data were applied to a Begum *et al.*, (2023) RPS algorithm to generate patient-level EQ-5D-3L utility estimates**

    - **As "change from baseline" data are not available at baseline, baseline utility estimates were generated by applying baseline VitoQoL scores to a Begum *et al.*, (2023) VitiQoL algorithm**

- **Next, least-squares regression analysis of the resultant dataset (pooled across TRuE-V1 and TRuE-V2) was used to estimate the importance of variables including F-VASI50, F-VASI-75 and F-VASI90 for change from baseline in EQ-5D-3L utility**

- **Finally, the parameter estimates from these analyses are used in combination with baseline EQ-5D-3L utility estimates (from the VitiQoL algorithm) to produce health state utility values for the CEM health states.**

- Bullet 1: This is correct.

- Bullet 2: This is correct.

- Bullet 3: Both the VASI (RPS) and F-VASI are measures of improvements from baseline in the Vitiligo Area Scoring Index. F-VASI has been deemed a good proxy for RPS on impact of quality of life to enable utility data estimation (Begum et al, 2023) (33).

- Bullet 4: This is correct.

- Bullet 5: As F-VASI is a change from baseline measure in itself, it is only reported as an improvement (i.e., post baseline visits), therefore baseline utilities could not be estimated from the VASI/RPS mapping algorithm and were estimated using the VitiQoL algorithm.

- Bullet 6: This is correct. For further explanation, see below:

    - 1. Post baseline utilities were derived from the VASI/RPS mapping algorithm (Begum et al, 2023) (33).
    - 2. Baseline Utilities were derived from the VitiQoL mapping algorithm (Begum et al, 2023) (33).
    - 3. Change from Baseline (CFB) in EQ-5D-3L utilities were modelled as outcomes against F-VASI 50/75/90 Responses (along with other covariates).
    - 4. Least Square Means in the CFB, were then generated for F-VASI 50/75/90 Responders and Non-Responders.

- Bullet 7: This is correct.

B14. Section B.3.4.3.1 of the company's submission states: *"F-VASI (DP[depigmentation]: -25%) is explored in scenario analyses, whereas F-VASI (DP: -50%) based estimates were not explored in the model due to providing estimates outside of the range of values suggested in the latest NICE technical support document for utilities."* Please can the company provide more information about the F-VASI (DP: -50%) based estimates, including specifically the F-VASI (DP: -50%) based estimates and the relevant range from NICE DSU TSD 22 referenced in the quote from the company's submission?

NICE DSU TSD 22 states that "The model should not generate predictions outside the feasible range of EQ-5D-3L. Model types that reflect the underlying distribution of EQ-5D-3L data will not predict outside the feasible range by design" (34).

When the F-VASI DP: -50% was explored in scenario analysis, the mean value was 0.815 at Week 24, and the min, max was -0.569, 0.939 (for the EQ-5D-3L Hernandez et al cross-walked utilities).

B15. Please provide interpretation of the estimated health state utility values applied in the company base case, tabulated below, in the context of (i) a general population utility estimate of 0.903 (3dp) for a 38-year-old (baseline age in company model is [redacted] years) member of the UK general population (source: https://eprints.whiterose.ac.uk/11096/1/HEDS_DP_09-11.pdf), and (ii) the description of burden of disease in Section B.1.3.1.2 of the company submission.

Deterministic health state utility assumptions in the company's model:

Description	Utility value
Baseline	[redacted]
No response	[redacted]
F-VASI50-74	[redacted]
F-VASI75-89	[redacted]
F-VASI90	[redacted]
Stable	[redacted]

Where a general population utility estimate of 0.903 is observed for a 38-year-old, it is not uncommon for utility values reported in RCT data to be higher than the expected population estimate. For example, if we consider the HI-Light trial, a pragmatic UK RCT where EQ-5D data was collected for patients with Vitiligo, EQ-5D utility values of 0.9287 and 0.9182 were reported for patients 9 months post treatment (Sach et al., 2021, Supplementary Table 3) (31).

In addition to this, uncertainty around mean predicted utility values for the UK general population are not reported in the cited source (Ara and Brazier, 2010) (35). Therefore, the plausible range of estimates with a degree of confidence (e.g., using 95% confidence or credible intervals) is unknown, in particular the plausible upper bounds.

In a separate publication (Janssen et al., 2021) (36), population utility estimates across 5 European countries including the UK, taking into account age and gender are reported along with estimates of variability, allowing for calculation of confidence intervals for the plausible range of values for utility estimates. An estimate of a Standard Deviation (SD) of around 0.171 (Table 3 of the reference) is reported. When this value of uncertainty is applied to the utility estimate of 0.903 for a 38-year-old, the 95% confidence interval (95% CI) is [0.893, 0.913]. When considering the entire

European population, the population mean for someone aged 38 is expected to be around 0.939 (Table 3 of the reference) (36). The 95% CI for this value, assuming the same SD of 0.171 is [0.929, 0.949]. This upper limit includes the values of 0.935 and 0.945 and are considered plausible estimates in a European population. This is consistent with the expected benefits of ruxolitinib cream across European populations.

The burden of disease is reflected in the utility estimates. Intuitively, it is observed that non-responders have the lowest EQ-5D utility value: patients classified as 'non-responders' have smaller treatment benefit compared to those who respond (F-VASI50/75/90 responders). The observed increasing trend in utility as treatment response increases is consistent with improvements in HRQoL measures also reported in this submission. The observed improvements from ruxolitinib cream underline the burden relief in this patient population. Details of the burden of disease are further highlighted in detail in Section B.1.3.1.2 of the submission.

There is no apparent reason why utilities should not decrease post baseline, particularly for patients not benefiting from treatment (i.e., non responders). Published studies do report utility decrements over time (e.g., Grandy et al. 2012) (37).

One plausible explanation as to why post baseline utilities are lower than baseline utilities for the non-responder group at week 24 (in the prior therapy sub-population as well as the overall population) is that the decrease (in post baseline utilities) is driven largely by the higher proportion of non-responders who were in the vehicle group. Around 82% of non-responders were in the placebo arm and 50% of non-responders were in the ruxolitinib cream treatment arm. It would therefore not be unexpected that vehicle non-responders have a deteriorating vitiligo condition over and above ruxolitinib cream non-responders. This is further reflected by the mean utilities for vehicle vs ruxolitinib cream as observed in Table 1 of the document supporting the response to this clarification question (please refer to the document titled 'Data to support the response of EAG clarification B15'). Mean reductions in change from baseline to week 24 utilities (mean CFB) also show differences between treatment groups for non-responders, with vehicle patients reporting larger mean CFB differences. This is further corroborated when considering other vitiligo or dermatology specific measures such as the VitiQoL and DLQI: 23% of vehicle patients reported

increased (worsening) VitiQoL total scores at week 24 in the non-responder group compared to 15% on ruxolitinib cream (in the non-responder group). Similar trends were observed with DLQI (total score) at week 24 (worsening score).

When considering non responders overall (ignoring treatment), patients with de-pigmentation (worsening of skin condition) reported poorer HRQoL in other measures (see Table 2 of the document supporting the response to this clarification question). As the mapping model implemented is based on percentage pigmentation values, patients with depigmentation will drive the utility value down, and this is also reflected in outcomes such as VitiQoL, DLQI and VNS scores (Table 2). For patients with depigmentation vs repigmentation: there were higher (worse) mean DLQI scores: 4.05 vs 3.74 and higher (i.e., worse HRQoL) mean VitiQoL scores: 39.23 vs 34.80. Patients who experienced depigmentation at week 24 also reported worse VNS outcomes: 22.5% vs 55% noted their vitiligo was 'less noticeable' or 'no longer noticeable' for de-pigmentation vs re-pigmentation (Table 2). Consequently, there appears to be strong alignment between HRQoL, clinical outcomes and mapped EQ-5D utilities.

B16. In a revised cost-effectiveness model, please incorporate utility and cost implications for the adverse event data in Table 24 of the Document B of the company submission (treatment-emergent adverse events occurring in ≥ 1% of patients in any treatment group). Please report utility, resource and cost data identification methods, and justify any assumptions required in absence of data.

Thank you for the suggestion. The model includes treatment-emergent adverse events (TEAEs) that occurred in ≥4% of patients in any group in the 24-week period corresponding to the double-blind period of the TRuE-V studies. In line with previous NICE submissions in dermatology (TA534 and TA681) (32, 38), only the cost impact of adverse events are considered in the model. This is also in line with the clinical validation conducted by the company (please refer to the summary of clinical validation provided as part of the responses to the clarification questions), which highlights that patients do not experience a detrimental impact to their quality of life (21). Thus, only the cost impact of adverse events impacting ≥4% of patients is captured. This enables the capture of relevant and realistic impacts that would be expected to be experienced

by patients and are likely of generating a cost impact on the NHS. The use of ≥ 1% would potentially lead to the capture of costs which would not be borne by the NHS.

Presentation of results

B17. PRIORITY. Documents A and B of the company submission report probabilistic cost-effectiveness results only, while the submitted cost effectiveness model contains probabilistic results that differ from those in Documents A and B. This is likely owing to the company rerunning the PSA before submitting, but leaves the EAG unable to validate results across the model and written documentation.

a. In a written addendum to Document B, please present and interpret deterministic base case cost-effectiveness results.

Please refer to the addendum attached to the responses to the clarification questions for the deterministic results and their interpretation.

b. Please can the company provide a copy of its model with the probabilistic base-case results aligned with Document B?

The model submitted for this appraisal was the list price version of the model whereas results presented in Document B are at PAS price. We have provided an updated version of the model at the PAS price with the probabilistic results aligned with those in Document B.

Section C: Textual clarification and additional points

C1. Please clarify the meaning of the superscripts in Table 14 of Document B — are footnotes missing? Similarly, please clarify the meaning of the asterisks in Table 37 of the same document.

Table 14 of Document B is taken from the EMA Opzelura assessment report (provided in the reference pack; Table 22) (12). Please see below for the text corresponding to the superscripts.

Error! Reference source not found. Multiple imputation: missing F-VASI score was imputed by fully conditional specification. The multiple imputation method uses treatment and observed stratification factors as predictors.

Error! Reference source not found. Response rate difference: SE of differences between response rates were from approximately normal distribution.

[c]Odds ratio: Exact logistic regression for Studies INCB 18424-306 and -307: [response at Week 24 = treatment + stratification factors (skin type Fitzpatrick scale Type I and II vs Type III, IV, V, and VI, region North America/Europe)]. Exact logistic regression for the pooled analysis: [response at Week 24 = treatment + stratification factors (skin type Fitzpatrick scale Type I and II vs Type III, IV, V, and VI, region North America/Europe)] + study.
[d]NRI: Missing postbaseline values were imputed as non-responders.
[e]Response rate difference: SE of differences between response rates were from approximately normal distribution.
[f] LOCF: For participants who were missing postbaseline values, the last observed non-missing postbaseline values were used to fill in the missing values at that visit.

Thank you for highlighting the use of asterixis in Table 37 of Document B. These asterisks can be considered to be surplus.

C2. PRIORITY. Clinical study reports (CSRs) for studies of ruxolitinib were missing from the company submission. These were identified by the company in the decision problem form as the key source of evidence for each study. Please can the company provide these along with all appendices/associated data tables (to include TRuE-v1, TRuE-v2, and the phase II trial).

Thank you for the request. These were provided to NICE on the 11th August 2023.

C3. PRIORITY. In addition to or alongside the request in C2, please provide a reference pack containing, within one folder, a PDF of each reference in Document B, numbered as per the reference list in Document B.

Please refer to the reference pack shared with NICE on the 1st September 2023. All provided references are named using the following structure: author surname, journal, and year. Further, they are provided as ‘publications, ‘data on file, ‘conference posters and abstracts’ and ‘other’.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	The Vitiligo Society
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The Vitiligo Society is a national charity headquartered in London and supports those living with vitiligo across the UK. Our mission is to beat vitiligo by eradicating the psychological, social and physical effects on people's lives and by finding effective treatments and a cure. The charity is funded by membership donations, fundraising, grants, and an online shop. We have approximately 800 members.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Grant of £17,275 from Pfizer paid in July 2022, awarded for The Vitiligo Society to undertake community research which is still being conducted.
4c. Do you have any direct or indirect links	n/a

with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	Previous surveys and general patient feedback.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	People living with the condition expressed vitiligo to have a huge psychological impact, especially if their patches are visible on their face and hands. People living with vitiligo often have two different perspectives on the condition. Some have accepted it after a long psychological and self-work process, but still wish they didn't have it. Others are still struggling with it and use camouflaging techniques to feel better and more confident. Both groups seem to have tried different treatments without success, some of them have resigned themselves to living peacefully with the condition.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Patients with this condition often feel unsupported and dismissed by GPs who lack specialized knowledge. Treatment options are limited and often ineffective, leaving patients feeling hopeless. They believe that there isn't enough focus on vitiligo, and hope for a more comprehensive and holistic service that offers support for the psychological side effects of the condition. People with vitiligo have limited treatment options and the only recommendation is to avoid sun exposure to prevent it from worsening. Many people find the cost and time requirements of treatments to be major obstacles to accessing them, as only those with significant financial resources and free time are able to receive the treatments properly.
8. Is there an unmet need for patients with this condition?	People with vitiligo often experience psychological effects that are not treated nor even mentioned when being diagnosed by a GP or healthcare professional. These side effects may include social rejection, identity loss, stress, humiliation, and impacts on self-image and self-esteem. Apart from the psychological aspect, many of them felt treatment options were very limited and weren't offered any options to stop the spread.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Higher re-pigmentation rates in comparison to existing treatments. Technology presents hope to patients who have long given up on the idea of being able to live a 'normal' life. An alternative to more extreme ‘treatments' that we know patients currently try (medical tattooing, skin bleaching).

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Technology marketed in the US has noticeable disclaimers on potential side effects – some of which may not be as relevant for topical treatment application. This may cause concern for certain patients. Technology only targeting those with non-segmental vitiligo in people 12 years and over. Potential cost to families if it is not approved on the NHS - this may prohibit many of those most in need from accessing it.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	This treatment could be beneficial for those who haven't found other options. Many express hope for new research to help them feel valued. Non-segmental vitiligo patients may find hope in this new technology.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Despite the patches being more noticeable in darker skin, it is recommended to offer vitiligo treatments to people with different skin types and colours. Given that everyone with vitiligo has its adverse effects, gender and other traits shouldn't be deciding factors.

Other issues

13. Are there any other issues that you would like the committee to consider?	n/a

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Vitiligo is often considered a cosmetic condition; this is not the case. In most cases vitiligo has a significant social and psychological impact on the patient and their quality of life. • Currently there are no effective vitiligo treatments available in the UK. This lack of treatment availability means patients often try unlicensed and potentially damaging products that they discover over the internet. Vitiligo patients are often preyed upon and exploited for financial gain with the promise of miracle results from untested / unlicensed and frankly dangerous treatments. • Technology is a huge development in the vitiligo community given higher expected re-pigmentation rates. • Technology should be accessible across differing socio-economic backgrounds. • Accurate and sensible information should be provided around potential side effects of technology.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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Please select YES if you would like to receive information about other NICE topics - YES or NO

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Single Technology Appraisal

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

Patient Organisation Submission

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- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	Vitiligo Support UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	We are a registered charity, funded by donations from the public. Our CEO has been involved as patient representative in: The production of the British Association of Dermatologists Guidelines for Managing People with Vitiligo (Eleftheriadou et al.; 2021; British Journal of Dermatology, Volume 186, Issue 1, 1 January 2022, Pages 18–29). The production of the British Association of Dermatologists and British Photodermatology Group Guidelines for Narrowband Ultraviolet B Phototherapy 2022 (Goulden et al.; 2022; British Journal of Dermatology, Volume 187, Issue 3, 1 September 2022, Pages 295–308). The production and editing of the British Association of Dermatologists/British Photodermatology Group/NICE kitemarked Phototherapy Clinical Standards. The Outpatient Recovery and Transformation Dermatology Working Group (NHS) Patient lead, the British Association of Dermatologists Patient Engagement Workstream and lay member of the Education Board. Participation and support in the establishment of the St John's Institute National Vitiligo Service and Registry. Our membership is currently 3,700 people who join us via our social media group on Facebook. We represent patients' views entirely in all the work that we do, and so our response below to the consultation comes from the patients' perspective.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder	No

list.] If so, please state the name of the company, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We are a small registered charity with a large and active group of people with vitiligo who are part of our charity through their membership of our private Facebook group (see above). We asked these questions of that patient group to gain their perspective of the current issues concerning the treatment of vitiligo and the impact that it has on them individually.

Living with the condition **6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?**	The aim of our charity is to create a space both for those who have found acceptance of their skin disease and also for those who struggle enormously with its impact in our appearance-oriented society governed by visual means of communication through social media. Firstly, that impact on patients relates to the difficulties in negotiating the system and being treated. There are enormous stresses getting access to treatment (for more, see below) currently in the United Kingdom. Secondly, there are also inherent difficulties that arise from the topical treatments generally prescribed being not specifically designed for what happens when the skin loses pigment in vitiligo. These are covered in more detail in the "Current Treatments" section below. Thirdly, in recent years, there has been increased visibility and coverage of vitiligo in the media. However, this increased visibility has yet to bring widespread acceptance of the disease in day-to-day life, both from the public towards patients and from patients towards their own skin. One might liken the impact of a very visible model having vitiligo to that of there being a film star who has Parkinson's disease or a model who has had a lower limb amputation. Their existence does show others that one can be successful with these diseases, and may raise awareness in the general public – the "Oh yes, what Winnie Harlow has" effect; however, these things do not change the difficulties of dealing with the disease in ordinary life and Winnie Harlow cannot help you gain access to secondary care or phototherapy treatment. Finally, vitiligo may not cause physical pain. This means that in general, in our current economic environment where GPs appear to take on the task of triaging patients for dermatology referrals, it is commonly dismissed as "cosmetic". This has caused patients more stress and distress. It is our fundamental belief that vitiligo should merit treatment because it causes a great deal of psycho-social distress in all aspects of daily life and carries with it a highly increased risk of concomitant autoimmune diseases. It also places a physical toll on patients in managing a high degree of photosensitivity and the risk of burning. A patient with vitiligo must be specifically advised on the use of sunscreens and managing exposure to the sun. Whilst there appears to be a lower risk of melanoma in vitiligo patients, they are still at risk of keratinocyte cancers, which are on the increase in the UK. The vitiligo patient also needs to be advised on managing the visual impact of their skin, if their level of distress warrants this. This involves the daily use of camouflage products or similar before leaving your home, to reduce the psychosocial impact of the white patches on your exposed skin. The vitiligo patient must also be aware, or made aware, of concomitant auto-immune diseases, specifically the risk of thyroid disease, where studies have reported an incidence of thyroid disease of up to 52% in patients with vitiligo (British Association of Dermatologists guidelines for the management of people with vitiligo 2021 (V. Eleftheriadou et al. 23 June 2021 https://doi.org/10.1111/bjd.20596). Yet many patients are reliant on charities or social media for information about vitiligo. This is in part due to health professionals who can be dismissive of the disease and, in particular, in speaking of its impact as purely "cosmetic" fail to appreciate the depth of its impact on people's psychological state and its hugely negative influence on the choices that people make in life. These are some of our members' experiences. **First of all, vitiligo's impact on appearing in public and socialising:** "I previously worked heavily in the small Asian community we have in my home town both in an official capacity as well a social and voluntary capacity. I now interact minimally with people outside my immediate family and very close friends. I have missed weddings, funerals, and birthday parties"; "It makes me depressed and stops me socialising properly, I am embarrassed and don't like people staring"; "I absolutely hate my vitiligo I'm actually tearing up writing this about how much I hate my body now, I hate looking at my patchy skin, I hate meeting new people. I fear my partner won't find me attractive anymore, I fear strangers will find me disgusting. I wear

	clothes that cover my vitiligo every day. I can't go out for dinner or drinks without two layers of fake tan and then I still see some of my patches through the tan"'. **On how you fit in in your family and culture:** "As a person of colour, I have to live with this every day and not just in the summer when I get a tan or go on holiday for a week…Looking so different to other members of your family is awful too, it robs you of your identity completely. It greatly affects my quality of life and interactions with work colleagues or new people"; "Now I watch me slowly ebb away to a white person I do not recognise in the mirror…". **On sports:** "Most painfully I have given up my football which I find particularly hard"; "It's stopped me going swimming as I used to love going underwater. I won't now in case my make up comes off". **And finally on the range of ways in which people can expect to enjoy their lives, including seasonal events (the impact of vitiligo being worse in the summer), social events and relationships including intimate relationships:** "I have also started to avoid summer get togethers with people, particularly those I don't see very often, because I no longer feel comfortable in my own skin in summer clothes where my vitiligo is on show for all to see. In short, I hate it and I want the old fun-loving me back. It's definitely changed me as a person and taken away a big chunk of my confidence and self-esteem"; "I spend my life living in fear. Fear of waking up in the morning with yet another patch and the stress and upset of trying to cover it up, the fear of developing other autoimmune diseases, the fear of strangers comments, the fear my children will be embarrassed of me when I collect them from school, the fear patients will refuse my care because of the way I look (I'm a student nurse), the fear my partner is not longer going to be physically attracted to me, the fear my children will develop vitiligo and go through what I do, the fear of summer and holidays when you know your spots will become more prominent"; "I feel people staring at me as I walk along the road"; "Vitiligo has made me lose my true self and feel down"; "I need to wear fake tan to be comfortable having intimacy with my partner or turn all the lights off". **Finally, whilst it is a chronic disease so one is required to manage its long-term existence, there is also a great deal of difficulty inherent in its unpredictability, with no clearly identified triggers for onset or new patches and no set trajectory of the disease; all of these also cause a lot of anxiety amongst patients:** "I spend a lot of time worrying about where it's going to spread to next on my body and how I will look in 5, 10, 15 years"; "For me living with a condition that can be unpredictable and disfiguring is stressful, the uncertainty of how my skin will look in months and years to come has been hard to manage as new patches appear. Unsurprisingly it's the vitiligo on the visible areas of my body that I find hardest to cope with"; "This is an awful, insidious disease as it is always changing". **Parents and carers also struggle with the impact on their children and the fear that a change of appearance may incite bullying or affect their self confidence:** "My beautiful 12yr old has become more aware of this awful condition and absolutely hates these visible patches. I cry inside every time I see a new one popping up knowing that a new conversation will be had where the question will always start with 'why mummy?' and its mine at night when she's fast asleep. Its not fair and I always wish that I could take them away and put them on me instead"; "My daughter who is 16 really struggles with her vitiligo. She dreads the summer and didn't go to prom because of it. It is heartbreaking for me as her mum as I just want her to enjoy her life".

	In summary, we are thrilled that public awareness of vitiligo is slowly increasing and, in some patients, there is more of a narrative around acceptance; however, as we see frequently amongst our members, many people simply cannot come to terms with it and struggle to live with the daily challenges in the absence of a safe, effective and accessible treatment.

Current treatment of the condition in the NHS7. What do patients or carers think of current treatments and care available on the NHS?	First of all, we would like to quote Bergqvist and Ezzedine ("Vitiligo: A Review" (Bergqvist and Ezzedine Dermatology 2020; 236:571–592), "Vitiligo should not be dismissed as a cosmetic or insignificant disease, as its effects can be psychologically devastating, often with a considerable burden on daily life". Secondly, we agree with their contention that, "[t]he treatment of vitiligo is still one of the most difficult dermatological challenges. An important step in the management of vitiligo is to first acknowledge that it is not merely a cosmetic disease and that there are safe and effective treatments available." However, patients' experiences of getting treatment in the UK are: 1. Varied to a great and unacceptable degree, over and above the inevitable individual differences between Integrated Care Systems and despite the clear guidance that is readily available and provided by the Primary Care Dermatology Society; the British Association of Dermatologists Guidelines for Managing People with Vitiligo (Eleftheriadou et al.; 2021; British Journal of Dermatology, Volume 186, Issue 1, 1 January 2022, Pages 18–29) and the NICE Clinical Knowledge Summaries: Vitiligo; 2. Dependent on individual GPs' personal approach to treating this disease (for more, see patients' comments below); 3. Often terminated in primary care and denied access to secondary care; 4. Dependent in secondary care on a consultant dermatologist's interest in the disease or their being prepared to treat, and/or refer onward to phototherapy; 5. The first line topical treatments available, either a potent or very potent steroid or an immunomodulating ointment/ cream (tacrolimus/pimecrolimus), are not licensed for the treatment of vitiligo but, in the case of steroids, were developed for dermatoses (*A Treatise on Topical Corticosteroids in Dermatology* ed. Koushik Lahiri; Springer, 2018) and in the case of the immunomodulating creams were developed as an alternative to steroids for atopic dermatitis. The topical treatments have very variable rates of success. Tacrolimus is preferred for the face due to the skin thinning effects of topical steroids, and the face appears to respond better to treatment generally; 6. The most successful treatment for vitiligo currently is narrowband uvb. This is not available in primary care settings but only through referral to secondary care which thus requires vitiligo patients being given equal access alongside skin diseases such as psoriasis and atopic dermatitis. Access to dermatology generally is currently subject to very long waiting lists (e.g., for the University Hospitals Bristol and Weston, the initial wait is 29 weeks). Then, there is the considerable inconvenience and the **unseen cost** in following the course of phototherapy treatment, which may take up to a year, may constitute at least two appointments a week and thus must be fitted around work, education or family life. As a result, many of our members resorted during COVID-19 to buying their own handheld narrowband-uvb devices to treat small areas of vitiligo at home. The costs impact on missing work, education, the costs of travel, parking and ancillary costs such as purchasing a UVB handheld unit. These do not appear in calculations of patients treated, we believe, which are taken from statistics of coded treatment within the NHS but should be factored in for a condition that is frequently denied access to treatment; 7. The two topical treatments have their own side effects with long-term use, which is generally required due to the tenacious nature of vitiligo. In fact, recent research in the United States has shown that the skin cells affected by vitiligo appear to have a "memory", so the disease **frequently** returns after treatment, even if it has been initially successful (The Role of Memory CD8+ T Cells in Vitiligo Rebecca L Riding, John E Harris *J Immunol* 2019 Jul 1;203(1):11-19. doi: 10.4049/jimmunol.1900027);

8. Many people wish to begin using ruxolitinib/Opzelura. However, it is currently only available privately and the cost of the prescription alone, which is estimated to be around GBP 1000 per month, is beyond the reach of most patients with whom we have contact;
9. Finally, there are very limited psychodermatology services available in the NHS. Depression has been found to be a key part of the vitiligo disease profile ("Patients with vitiligo were significantly more likely to suffer from depression. Clinical depression or depressive symptoms can be prevalent, with the actual prevalence differing depending on screening instruments or, possibly, geographical regions. Clinicians should actively evaluate patients with vitiligo for signs/symptoms of depression and provide appropriate referrals to manage their psychiatric symptoms accordingly" Vitiligo and depression: a systematic review and meta-analysis of observational studies Y.C. Lai, Y.W. Yew, C. Kennedy, R.A. Schwartz British Journal of Dermatology, Volume 177, Issue 3, 1 September 2017);
10. This means that patients who are finding their vitiligo very difficult to manage have to join the waiting lists for general psychological support in primary care, rather than accessing a specialist service that understands the impact of changed appearance and managing a chronic disease.

In light of these difficulties, these are some of the experiences of our members in relation to trying to gain access to treatments and to the success of those treatments: "I saw a dermatologist when I was 11/12 who kept calling it psoriasis (I do not have that by the way), offered me a steroid cream with no direction at all. I have had PUVA light treatments, 3 times a week, drove 30 minutes each way for around 20 seconds of treatment with no effects. So, sadly, no positive answers from me other than trial and error of fake tans and camouflage over 30 years. One positive was that my local hospital had a camouflage specialist when I was young who helped me mix my camouflage colours to match my olive skin tone but this facility is a rarity sadly…";

"When I was originally diagnosed, I seen a dermatologist who confirmed vitiligo. I was given some creams to try with no effect. I then got discharged and told to return if it spreads to my face so get referred to a camouflage specialist. No other treatments were offered, no sun exposure advice. From my own research it seems the treatments available are very time consuming and have a low success rate of repigmentation";

"Steroid cream and Protopic rarely work but are also rarely offered. I found with GPs I have to tell them what I need and then they 'google' it. I was lucky to have light therapy a few years ago but it was a 1.5 hours round trip 3 times a week for nearly a year. If I didn't work for myself now, I would never have been able to commit to that much time. It cost a lot in terms of jobs I couldn't take on during that time, fuel and hospital parking. It had some good success to start with but then I burned and they had to stop and all the pigment soon left again. I have since used a handheld device that I purchased myself and saves a lot of time but again I have to endure the in between where I look worse before I look better and then the inevitable depigmentation that returns a few months after stopping the light therapy."; "I have been left with horrible stretch marks that are now 44 years old from when I was a child using steroid creams on my legs and hips. Then as an adult taking psoralen and uva treatment took up much if my time and made me feel so sick, yet I was grateful to be given some pigment back. However, this did not last. Going back to the Drs after a couple of years, I found out I was not allowed any further PUVA treatment on the NHS"; "I was literally given nothing, GP referred me to dermatologist who basically said nothing they can do, gave me Protopic, which didn't work ... no cure they said, need to try and live with it, no psychological support offered, which I believe it should be some people can accept but there are others that can't accept or love the patches"; "I found from a friend that a regional hospital was treating vitiligo patients. I was able to persuade my GP to refer me to dermatology. I had light treatment, which did not work, I was prescribed Tacrolimus which did initially work on parts of the face. It seemed to reduce spread rather than enable re pigmentation. Some GPs were very reluctant to prescribe the medication. My skin eventually became sensitised to tacrolimus. I have not used any medication for a number of years and the loss of

	pigment has greatly increased. I would like to see a dermatologist again to look at the skin growths I have recently acquired in the areas that became sensitised. My present GP is a significant barrier"; "My Vitiligo never even been put on the system how many times I mentioned that to GP, as I do believe I am struggling with other immune disease, caused by Vitiligo. Really have to push to do just basic blood tests, and this year they just decided to put me on antidepressants, and I never ever mentioned anything related to depression! I definitely don't need them, and NOT going to take them. Very disappointed"; "When I was originally diagnosed, I saw a dermatologist who basically said there's no cure - and prescribed a cream - Protopic I think - but as it was around my eyes, I read too many scare stories so I stopped using it after a few weeks. All my research has been off my own back as I know there's nothing that can be done and GPs don't really want to know"; "I was unable to get a referral to dermatology as it wasn't impacting my life enough. I was told my vitiligo wasn't that bad. I was given Protopic but I had to beg for this, unfortunately did not do anything to help. I also asked about sun cream as I wanted this on prescription to make sure I was properly protecting my skin and I was told just to buy a factor 50 in the supermarket. I feel like my vitiligo was not taken seriously, my doctor did not understand how this effects me and did not try to think out the box at different treatment options or for referrals to dermatology. My vitiligo has now spread and worsened although I've not been back to the doctors as they made me feel so silly, inconvenient and like I was bothering them the first-time round"; "GP immediately referred me to dermatology and gave me a steroid cream to use while I was waiting. However, the instructions for the steroid cream were incorrect according to dermatology (he'd told me to mix it with a moisturiser). Dermatologist was quite dismissive, there's not much we can do, nothing really works but we can try a different steroid cream see if it slows it down. Also gave me a leaflet on vitiligo and treatment options. I was nervous about using the steroid cream but tried it for a couple of weeks. I found it made my skin super sensitive to the sun (5 mins outside and I felt like my hands were on fire) so stopped using it. Went back for follow up and they gave me Protopic to try but I'm not very clear on how to use and nervous about side effects so haven't used. Also, dermatology seem to be leaving it to me to determine if treatment works or not. On second appointment they advised me to take pictures of the affected areas. I've decided just to live with it and not bother".
8. Is there an unmet need for patients with this condition?	We definitely think that there is an unmet need for a treatment for vitiligo. The most common experience within our membership is that people have struggled to gain access to treatment, and that if they are successful in getting access, the treatment has limited success (possibly due to not being specifically licensed for our disease) and there is a high risk of recurrence of patches. This would be the first treatment that tackles the molecular/cytokine action of vitiligo. It is based on many years general research into JAK inhibitors, and a particular interest in the US in their use in tackling skin diseases such as vitiligo and alopecia. There are significant difficulties for vitiligo patients in being believed about the impact of the disease on their lives, in acting as advocates for themselves with their doctors to prevent them from being dismissed, and in being persistent in that advocacy beyond primary care into secondary care. To have this successful treatment available in primary care would liberate a large number of vitiligo sufferers in the UK. It would allow their disease to be treated as the chronic disease that it is, and would allow them some control over their lives. It is long overdue, and many people are waiting impatiently to be able to take treatment back into their own hands again, and not to be rebuffed, belittled, dismissed and thwarted in their quest to overcome the destruction of their appearance and their identity.

Advantages of the technology. What do patients or carers think are the advantages of the technology?	There is a lot of hope amongst our membership that this might become available, many of whom have faced a lot of knockbacks along the way to trying to reverse their depigmentation. Some comments include: "It strikes me that this would be far less aggressive than the light treatment I'm constantly subjecting my skin to. It seems to have much better results than previous creams that have been subscribed. It sounds very hopeful that a lot of patients' skin would respond well to this. For me, personally, if I could use this and it worked, it would be a game changer for me. I feel I would get the old me back and get my old life back that I used to enjoy so much"; "It has been shown to have the greatest success rate of any treatment thus far"; "Think the results from tests were good but not holding much hope to getting it but wouldn't it be nice to have a remedy to try"; "It is the first treatment ever available for vitiligo so I personally can not wait to try it. I understand that it is not a cure, but I am so excited and nervous at the same time...but will not be able to afford it if it is not available on the NHS"; "It seems to have a success rate, which I have only read as I am in UK and not available but hoping what I read is true and a breakthrough and approved on NHS"; "Children can grow up without having to deal with the weight of vitiligo"; "Only ever reading articles about this "miracle cure" from what I've read it's a game changer and I really hope and pray this becomes available in the UK".
Disadvantages of the technology10. What do patients or carers think are the disadvantages of the technology?	The most frequently reported side effects of Opzelura in the manufacturer's published trial data included acne (5.9% of trial cohort in Double-Blind period, 1.5% ruxolitinib cream, "Two Phase 3, Randomized, Controlled Trials of Ruxolitinib Cream for Vitiligo" David Rosmarin, M.D. et al., *NEJM* October 20, 2022 vol. 387 no.16) at the site of application and pruritis (5.0% of trial cohort in Double-Blind period,1.5% ruxolitinib cream, as previous). The results have been read in journal report by us, and it should be noted we are not clinicians. Because Opzelura (the brand name of the technology) is currently only available on private prescription at a cost that is beyond many vitiligo patients (see above), the answers to this question from patients focus primarily on the current situation when the cream is outside the financial reach of many of the respondents, and, as of yet, most respondents have not been able to experience its benefits, unlike patients in the US and Europe: "The disadvantages that I see is that it must be used long term to maintain results but for me that would be worth it to keep the vitiligo away once and for all. The other side is cost. If NICE don't approve it under NHS, it will only be a small minority of the very wealthy that can afford to try it and the rest of us will be left to continue to deal with the disease just like before"; "The price of it, if it is not available on the NHS. I would be willing to use it long term to maintain my regained pigment"; "Suppressing the immune system over a sustained period will have side effects on the skin. It will be a balance that requires monitoring"; "If it helps and the side effects are minimal than there should be no disadvantage except the cost". We conducted an informal poll of the three principal side effects taken from the NEJM trial paper. These are acne and pruritis at the site of application and an increased tendency to nasopharyngitis. Overall, the responses indicated (figures available on request) that people would be willing to accept the side effects given the benefits of the cream in treating their vitiligo and that they would tolerate topical side effects in order to regain themselves again, the person who they feel has died to them because of their vitiligo.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	There are no groups that we are aware of that would be affected in this way.
Equality **12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?**	Whilst vitiligo can have a significant impact on all skin colours, there is an additional cultural burden that may be experienced in skin of colour.
Other issues **13. Are there any other issues that you would like the committee to consider?**	I have had vitiligo for 19 years, and I have worked for patients with vitiligo for the last 10 years. Through Vitiligo Support UK, I have tried to provide a means with which patients can advocate for the treatment of their skin disease, and to support them in their moments of anguish, and their low points of self-consciousness and shame, as well as celebrating with those who have reached the point of acceptance of their vitiligo. I have also worked with the BAD to provide Guidelines that allow clinicians to understand the existing scientifically proven treatment steps that can be taken for patients with vitiligo. There is a deep frustration at the heart of our community. We are seen (and are constantly commented on or stared at) day to day and must manage that all the time, even when we go to bed with an intimate partner, but we are not “seen” by our GP or dermatologist. In a period of time where social media in various forms has brought enormous pressures on everyone’s appearance, it is extremely hard to look “different”. This technology is a treatment that works, as the research undertaken demonstrates. It is a treatment that works for our specific disease. We have never had such a thing before, and many vitiligo patients, from the suicidal young man who no longer plays the football that he loves, to all those who have to literally and figuratively “put a brace face on it” every single day, long for this treatment. Please see us. Please listen to the voices of the people who’ve spoken above and all those who wait in the sidelines. We are part of the NHS and its current principles of universal healthcare. We are part of your community, though you may not know it as so many of us feel driven to hide our skin disease from others. Please consider our needs now, and approve this technology for us.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Treatments exist for vitiligo but are unlicensed and limited in effectiveness, for example, patients must follow several courses of inconvenient phototherapy with long term risk to skin health and their vitiligo is at high risk of returning; • Vitiligo is an autoimmune disease and carries a concomitant risk of several other diseases, including a high risk of thyroid disease; treating it brings patients into the medical practice to be monitored for these attendant illnesses; • Patients suffer deeply psychologically from the change in their appearance, change in cultural and social identity, daily impact on a wide range of "social transactions" including intimacy and the loss in control that the disease, vitiligo, brings; • There is a shocking lack of knowledge or appropriate patient-handling skills amongst primary care physicians about this disease and a constant story of being personally dismissed by doctors; • This treatment is a first in many, many years as a treatment for vitiligo, and it brings hope for patients that they can be freed to be the person they once were by restoring the pigment in their skin. This is a very important thing for many vitiligo patients. Please see their needs.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	British Association of Dermatologists
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes ~~or No~~ A specialist in the treatment of people with this condition? Yes ~~or No~~ A specialist in the clinical evidence base for this condition or technology? Yes ~~or No~~ Other (please specify):
5a. Brief description of the organisation (including who funds it).	The BAD is a not-for-profit organisation whose charitable objectives are the practice, teaching, training, and research of dermatology. It works with the Department of Health, patient bodies and commissioners across the UK, advising on best practice and the provision of dermatology services across all service settings. It is funded by the activities of its members.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No.
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aims are: 1) Repigmentation (return to original colour) of skin affected by vitiligo; OR 2) Stopping the progression of vitiligo. Additional aims include: 3) Improving the quality of life in people with vitiligo. 4) Reducing the psychological distress in people with vitiligo.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	1) Repigmentation (return to original colour) of treated area of skin affected by vitiligo by at least 75%; OR by Vitiligo Noticeability Score [VNS] score of 4 or 5, i.e. vitiligo is a lot less noticeable or no longer noticeable, respectively) Eleftheriadou *et al.* https://academic.oup.com/bjd/article-abstract/180/3/574/6749808. OR 2) Stopping the progression of vitiligo. Significant response also include: 3) Improving the quality of life in people with vitiligo. 4) Reducing the psychological distress in people with vitiligo.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, there is. Currently, there are no licensed treatments for vitiligo available to patients on the NHS. Recently, ruxolitinib cream has been approved by the MHRA, however, it is only available in the private sector in the UK at present. Topical treatments such as corticosteroids (TCS) and calcineurin inhibitors (TCI; mainly topical tacrolimus) are used off-label and outcomes are often unsatisfactory. Phototherapy, which may be combined with topical treatments, require hospitals visit 2-3 times per week for up to 12 months; it may be difficult for many patients to commit to these visits. Excimer laser and surgery is not available in the NHS. Depigmentation (permanent removal of pigment) is only suitable for patients with universal vitiligo (affecting over 80% body surface area) and following careful psychological evaluation; it is only available in a few NHS departments of dermatology and unsuitable for the vast majority of vitiligo patients. Vitiligo is associated with psychological distress but psychological services are difficult for many patients to access within the NHS.

The aim of treatment for this condition

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	All patients with vitiligo require: 1) Sun protection (4-5* UVA, SPF 50 or more sunscreen) to avoid sunburn, with minimal sun exposure. 2) Psychological evaluation to identify level of psychological distress (mild, moderate or severe). If moderate or severe psychological distress is identified, patients should be offered referral to psychological services for further psychological evaluation and treatment. 3) Vitamin D levels should be checked in patients who are avoiding the sun. 4) All patients with vitiligo should be screened routinely for thyroid function and antithyroid antibodies. Incidence of thyroid disease in patients with vitiligo is up to 52% and patients with vitiligo are at increased risk of Graves disease and even thyroid cancer. 5) All patients with vitiligo should be offered cosmetic camouflage. First-line treatments (off-label) include TCS and TCI (mainly topical tacrolimus for the face); however, the results of these treatment options are often unsatisfactory. Other treatments include (mainly) whole-body or localised phototherapy (as monotherapy or combined with TCS or TCI), which is only available in secondary care and requires 2-3 weekly hospital visits for up to 12 months. Depigmentation (permanent removal of the remaining pigment) is only suitable for a small number of patients with universal vitiligo (i.e. vitiligo which covers over 80% of the total body surface area) and following careful psychological evaluation. This intervention is only available in a handful of NHS hospitals and it not suitable for the majority of people with vitiligo.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	British Association of Dermatologists guidelines for the management of people with vitiligo 2021 https://academic.oup.com/bjd/article/186/1/18/6593593
9b. Is the pathway of care well defined? Does it vary or are there differences of	Current clinical management of vitiligo often includes either no treatment (due to variability of currently available treatments results and accessibility issues) or topical treatments as first line. The usual pathway for patients with vitiligo include initial review by their GP, who will refer to secondary care for further management and in some

opinion between professionals across the NHS? (Please state if your experience is from outside England.)	cases will initiate a short course of TCS. Unfortunately, in the current climate of NHS crisis, dermatology waiting lists vary between 12-24 months for general dermatology clinics. In addition, once seen in secondary care, many patients with vitiligo are unable to start phototherapy either due to long NHS waiting lists for this treatment option (over 1 year at some centres, following first assessment by a dermatologist), and/or personal time constrains (i.e. the need to attend 2-3 times a week for up to 12 months). Furthermore, many NHS dermatology departments either offer phototherapy to a very limited number of vitiligo patients or not at all due to constraints on phototherapy services. As such, patients with other dermatological diseases (such as eczema or psoriasis) who usually require shorter courses are prioritised instead.
9c. What impact would the technology have on the current pathway of care?	Vitiligo is a debilitating and psychologically devastating skin disease, which usually appears in the young population. Vitiligo is an autoimmune disorder that is often associated with other autoimmune diseases and requires patients to avoid the sun and/or risk sun burns with minimal sun exposure; therefore, there is an urgent need for an effective and licensed treatment for vitiligo patients in the UK. Current clinical recommendations for the management of vitiligo are based on trials of poor to moderate quality. Due to the lack of licensed treatments for vitiligo, and the fact that usually first line treatment for vitiligo includes topical preparations (TCS or TCI), ruxolitinib would fit into the first line treatment category alongside TCS and TCI and perhaps following a short trial of TCS or TCI
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	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 TCS or TCI.
10a. How does healthcare resource use differ between the technology and current care?	Currently, vitiligo patients receive suboptimal care and have increased number of primary care encounters, more time off from work and higher unemployment rates (Thompson *et al.* 2022 10.1192/bjo.2022.591). They can potentially incur substantial out-of-pocket expenses, such as skin camouflage and sunscreen. It is anticipated that ruxolitinib cream will achieve more successful repigmentation resulting in decrease in clinical encounters and improvement in quality of life.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Ruxolitinib cream is a topical preparation and vitiligo is the most common pigmentary disorder of the skin; therefore, it should be available in secondary care. Vitiligo patients are seen on the NHS in general dermatology clinics, rather than specialist clinics across the UK.
10c. What investment is needed to introduce the	None needed. Infrequent blood test monitoring (FBC/lipids) *may* be required whilst on this treatment.

technology? (For example, for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, based on the phase 3 trials, the results are satisfactory and were meaningful to patients and clinicians (based on VNS and VASI outcome measures, respectively).
11a. Do you expect the technology to increase length of life more than current care?	No, as vitiligo does not affect the length of life of its patients, however, it has detrimental effects on the quality of life and mental health of people with vitiligo.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Repigmentation of vitiligo patches is one of the critical outcomes recommended by patients and clinicians to be measured in all clinical trials. Furthermore, three large international workshops with patients with vitiligo and their parents/caregivers were conducted to define successful repigmentation from the patients'/carers' points of view and to propose how and when repigmentation should be evaluated in clinical trials for vitiligo. Results revealed that both an objective and a subjective scale to measure repigmentation should be used. In particular, alongside percentage of repigmentation (objective scale), a subjective, patient-reported scale such as Vitiligo Noticeability Scale, should be used (Eleftheriadou *et al.* 2019 https://doi.org/10.1111/bjd.17544). A recent retrospective, observational study using UK general practice data (2004–2020) revealed that people with vitiligo have a higher incidence of recurrent depressive disorder (RDD) and anxiety disorder compared with control groups, and this increase in the risk may be greatest in Afro-Caribbean and other minority ethnic populations. In addition, people with vitiligo and psychological comorbidity had more primary care encounters, more time off from work and higher unemployment (Thompson *et al.* https://doi.org/10.1192/bjo.2022.591). Finally, some quality-of-life measures may not adequately capture the impact of living with skin condition such as vitiligo, as skin in patients with vitiligo is not usually sore or painful (unless sunburned). In addition, they may not capture anxiety and depression, hence patients with vitiligo often "score" lower in these measures compared with patients with other health and skin conditions. Finally, it is likely that treatment with ruxolitinib cream may result in substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Not aware of any.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	No practical implications or concomitant treatments are expected and the technology is expected to be equally easy to use as other currently available off-licence treatments.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Ruxolitinib cream should be initiated by a dermatologist, following confirmation of a diagnosis of vitiligo. Recently updated guidelines for vitiligo by the British Association of Dermatologists (Eleftheriadou *et al.* 2022 10.1111/bjd.20596) suggests that early treatment of vitiligo seems to be more efficacious compared to treatment of long-standing disease; therefore, there is an urgent need for an efficacious, topical treatment for vitiligo, which would not require multiple hospital visits over a long period of time.

	In addition, BAD guidelines recommend that any treatment should be continued for at least 3-4 months; should there be a positive response (i.e. some evidence of return to original skin colour in the areas treated), the treatment should continue for longer (i.e. additional 3-4 months at least) and then re-evaluated. Blood test monitoring (FBC/lipids) *may* be required whilst on this treatment due to reports of neutropenia and thrombocytopenia with topical ruxolitinib. These are rare, however, patients may need monitoring initially depending on risk factors. Follow-up with a dermatologist should be conducted after 3 months, as is done for other vitiligo patients on topical treatment and/or phototherapy to assess response and monitor for any side effects. Once complete repigmentation has been achieved, stopping treatment or switching to a maintenance regimen could be considered.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	See section 11b.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes, as current clinical recommendations for the management of vitiligo are based on clinical trials of poor to moderate quality. As previously mentioned, there is no licensed treatment for vitiligo available on the NHS in the UK and results of currently available treatments on the NHS can often be unsatisfactory. Vitiligo is a highly visible, debilitating and psychologically devastating skin disease, which usually appears in the young population. Vitiligo is an autoimmune disorder that is often associated with other autoimmune diseases and requires patients to avoid the sun and/or risk sun burns with minimal sun exposure; therefore, there is an urgent need for an effective and licensed treatment for vitiligo patients in the UK.
16a. Is the technology a 'step-change' in the management of the condition?	Yes, as above, there is no licensed treatment for vitiligo available on the NHS in the UK 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.

16b. Does the use of the technology address any particular unmet need of the patient population?	Yes, as above.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The majority of side effects reported in the TRuE-V1 and 2, phase 3 trials, were minor (such as pruritus, application site acne) with only 14 out of 674 patients reporting as serious adverse events, which were deemed non-treatment-related.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes.
18a. If not, how could the results be extrapolated to the UK setting?	N/A
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Internationally agreed consensus on core outcomes set for vitiligo clinical trials include the following outcomes as essential: repigmentation, side effects and maintenance of gained repigmentation. Four items were further recommended for inclusion: cosmetic acceptability of results (measured by the Vitiligo Noticeability Scale), quality of life, cessation of spreading and tolerability or burden of treatment (Eleftheriadou *et al.* https://onlinelibrary.wiley.com/doi/abs/10.1111/pcmr.12354); therefore, the choice of outcomes is appropriate. In the TRuE-V1 and V2 phase 3 clinical trials, the outcomes measured that were in keeping with the internationally agreed consensus on core outcomes sets for vitiligo were as follows: 1. Repigmentation measured by an objective scale such as Facial and total vitiligo area scoring index (F-VASI and T-VASI, respectively. 2. Cosmetic acceptability of results as measures by patient-reported outcome measure: Vitiligo Noticeability Scale (VNS) and Colour matching (excellent, very good, good, poor or very poor)

	3. Quality of life. 4. Adverse effects of the intervention.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	As above.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not aware of any.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Not aware of any.
20. How do data on real-world experience compare with the trial data?	No real-world data is available yet.

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	As vitiligo develops before the age of 20 in about 50% of patients, making the treatment available for children is particularly important. Although more noticeable in people with darker skin tones, vitiligo affects people with all skin tones and can be psychologically devastating, regardless of the patient's skin colour. Also, vitiliginous patches burn easily in the sun regardless of the patient's original skin tone.
21b. Consider whether these issues are different from issues with current care and why.	N/A

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• Vitiligo is a highly visible, debilitating and psychologically devastating skin disease, which usually appears in the young population. • Vitiligo is an autoimmune disorder that is often associated with other autoimmune diseases, and requires patients to avoid the sun and/or risk sun burns with minimal sun exposure • Current clinical management of vitiligo often includes either no treatment (due to variability of currently available treatment results and accessibility issues) or topical treatments as first line. • There is no licensed treatment for vitiligo available on the NHS, and currently available (off-licence) treatment options for vitiligo are often unsatisfactory. • There is an urgent need for an efficacious, topical treatment for vitiligo, which would not require multiple hospital visits over long periods of time and could be prescribed to both children and adults as soon as they are diagnosed with vitiligo by a dermatologist.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Clinical expert statement

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In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also

send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **29 December 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

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

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

NICE National Institute for Health and Care Excellence

Part 1: Treating vitiligo and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Jonathan Batchelor
2. Name of organisation	King's College Hospital NHS Foundation Trust
3. Job title or position	Consultant Dermatologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with vitiligo? ☒ A specialist in the clinical evidence base for vitiligo or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for vitiligo? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To make the condition less noticeable, by encouraging repigmentation in affected areas of skin.

9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Either a 75% improvement in repigmentation or an improvement in the noticeability of the affected areas of vitiligo (ideally measured with a validated scale such as the Vitiligo Noticeability Scale)
10. In your view, is there an unmet need for patients and healthcare professionals in vitiligo?	Absolutely. The only licensed treatment for vitiligo in the UK is cosmetic camouflage. Topical corticosteroids and topical calcineurin inhibitors are the first line treatment used most often, but these only help in a small number of people. Those with more extensive vitiligo are sometimes referred for narrowband UVB phototherapy but access to this is limited in some areas of the UK and it is usually given in a hospital, which is very time consuming. The psychological impact of the condition is considerable and access to psychological services is extremely limited in the UK.
11. How is vitiligo currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Yes, there is a guideline that has been produced by the British Association of Dermatologists. This provides a framework for initial treatment of the condition, including conservative measures such advice about sun protection, followed by initial topical treatment with topical corticosteroids or calcineurin inhibitors. However, as mentioned above, these treatment only work in a small number of people and work better on certain anatomical sites (face and neck). The technology would be very welcome addition to the current treatment pathways, as it could be prescribed early on in the treatment pathway and would not necessarily need to be prescribed by secondary care clinicians. Early treatment is important because this has been shown to slow the progression of the condition, and vitiligo is more responsive to treatment if the treatment is started early.

	Even though the above treatment pathways exist, many people with vitiligo feel that they are treated rather dismissively by some GPs and other healthcare professionals, due to the perception that no effective treatment exists for the condition. The technology is an easily prescribed topical treatment, which has been shown to be very effective. If available, healthcare professionals could offer the treatment to patients very easily, avoiding the previous nihilistic attitude towards treating the condition. The treatment would also reduce the number of people with vitiligo who have to be referred on to secondary care for phototherapy, which would bring about significant cost savings. In short, it would have a huge impact on the current pathway of care.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The technology is very similar to the treatments currently used in current clinical practice, in that it is a simple topical treatment applied to the skin. Prescribing the treatment would be very similar to the prescribing of current topical treatments, and this could be done in primary care. No specific investment in facilities or equipment would be needed to allow the technology to be introduced. Any healthcare profressionals prescribing the treatment would need to be aware of the side effects of treatment (mostly mild infections, although some rarer side effects such as blood clots and raised cholesterol have been described).
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, definitely. The treatment has been shown to bring about much greater rates of repigmentation in vitiligo than other currently used topical treatments such as

• Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	topical corticosteroids, and with fewer potential side effects such as skin thinning. This will help to make the vitiligo less noticeable. Vitiligo does not have an impact on length of life so the treatment will not have any impact on length of life. However, it will certainly increase the impact of vitiligo on the quality of life of those who have it (the condition has been shown to have considerable impact on quality of life and on mental health)
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No. Vitiligo affects people of all skin types and can have the same psychological and quality of life impact in people of any skin colour. There is nothing to suggest that the effectiveness of treatment would be different in any particular group of people who might use it (with the exception of those with segmental vitiligo, which tends to be much less responsive to treatment).
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	It is a simple topical treatment, which can be applied to the skin easily. This is as easy to use (but more effective) than the usual first line topical treatments (topical corticosteroids or calcineurin inhibitors). It is easier, safer and less time consuming to use than second line treatments such as phototherapy (which entails trips to hospital to receive ultraviolet light treatment) and potentially even more effective as well.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No, other than to stop using the treatment if there has been no improvement after daily use for 3 months or so.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen	Many quality of life instruments are not sensitive enough to detect improvements in quality of life caused by skin conditions, especially those for which the main impact is the appearance of the skin (as is the case for vitiligo). There are more specific quality of life measures which are more helpful in this respect, such as the VitiQoL (Vitiligo Quality of Life Index) and the Dermatology Life Quality Index (DLQI). Mental health measures are also important when assessing the impact

may be more easily administered (such as an oral tablet or home treatment) than current standard of care	of vitiligo treatments, due to the disproportionate effect it can have on the mental health of those who have the condition.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes. It is much more effective than the traditional first line topical treatments. Having an effective treatment like this available will change the way in which health professionals approach the treatment of people with vitiligo, moving away from an attitude of nihilism and occasional dismissiveness to one of hope and positivity.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side effects of the treatment are few and generally very mild (e.g. infections, application site reactions). These are unlikely to have a significant effect on quality of life.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes, the clinical trial participants were representative of those who would receive the treatment in the UK and the way in which the treatment was given in the trials is representative of how it could be used in UK clinical practice. Outcome measures used in the trials were relevant.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
22. How do data on real-world experience compare with the trial data?	The treatment is relatively new and so real world data are fairly limited.
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any	The condition can affect all people, regardless of skin type, and although the noticeability can be greater in those with darker skin types, it can have a

potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	considerable impact in those with lighter skin types as well. However, there are sometimes cultural factors in those with darker skin types which lead to them experiencing a greater level of discrimination if they have vitiligo (for example, it is sometimes mistaken for leprosy and this can lead to them being discriminated against). As such, this new treatment can have a particularly positive impact for those who might be at risk of greater discrimination due to them having vitiligo.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

The treatment is a simple topical treatment, which can easily be applied to the skin

The treatment is safe and much more effective than currently used topical treatments

The treatment is as effective or even more effective than costly and time-consuming phototherapy, which requires secondary care referral

The treatment could be used easily in a primary care setting and could avoid referrals to secondary care

Vitiligo can have a considerable impact on the quality of life and psychological wellbeing of those who have the condition, especially for those with darker skin types, and the treatment will be particularly beneficial for those who might experience discrimination due to having vitiligo

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Single Technology Appraisal

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

Clinical expert statement

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **29 December 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

NICE National Institute for Health and Care Excellence

Part 1: Treating vitiligo and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Viktoria Eleftheriadou
2. Name of organisation	British Association of Dermatologists
3. Job title or position	Consultant Dermatologist and Associate Professor
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with vitiligo? ☒ A specialist in the clinical evidence base for vitiligo or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for vitiligo? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The main aims are: 1) Repigmentation (return to original colour) of skin affected by vitiligo; OR 2) Stopping the progression of vitiligo.

	Additional aims include: 3) Improving the quality of life in people with vitiligo. Reducing the psychological distress in people with vitiligo.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	• Repigmentation (return to original colour) of treated area of skin affected by vitiligo by at least 75%; and by Vitiligo Noticeability Score [VNS] score of 4 or 5, i.e. vitiligo is a lot less noticeable or no longer noticeable, respectively) Eleftheriadou *et al.* https://academic.oup.com/bjd/article-abstract/180/3/574/6749808. OR/AND • Reducing the psychological distress in people with vitiligo or Improving the quality of life in people with vitiligo. Significant response also include: • Stopping the progression of vitiligo.
10. In your view, is there an unmet need for patients and healthcare professionals in vitiligo?	There is currently an unmet need for licensed and effective treatment option for vitiligo, which would be easily accessible for those, who wish to treat their vitiligo. Currently available (off label) treatment options for vitiligo are often unsatisfactory and include tacrolimus, topical corticosteroid, and phototherapy. In particular, topical corticosteroids effectiveness for vitiligo is only 20%. The most effective treatment, which is currently available for vitiligo in the UK, is a combination of topical corticosteroid and phototherapy; its effectiveness rate is around 27%, which is still low. Phototherapy is only available in the secondary care and requires patients to attend the hospital 3 times a week for 9 to 12 months continuously. This leaves patients unable to attend hospital phototherapy due to work and/or school commitments. Unfortunately, in the current NHS crisis, (non- skin cancer) dermatology waiting lists vary between 1-2 years. Several hospitals in the UK have stopped accepting referrals for phototherapy for patients with vitiligo altogether because

	their treatment usually requires prolonged courses and is a burden for the NHS. Understandably, this fact leaves vitiligo patients extremely disappointed, disadvantaged and deprived of treatment options. In addition, vitiligo is associated with psychological distress, but psychological services are difficult for many patients to access within the NHS.
11. How is vitiligo currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Yes, British Association of Dermatologists guidelines for the management of people with vitiligo 2021 have been recently published. https://academic.oup.com/bjd/article/186/1/18/6593593 Current clinical management of vitiligo often includes topical treatments (such as topical corticosteroids or topical calcineurin inhibitors) as first line. Second line treatment, normally include phototherapy combined with topical treatments. However, this treatment (phototherapy) is not available in many NHS hospitals. When phototherapy available, many NHS dermatology departments either offer phototherapy to a very limited number of vitiligo patients or not at all due to constraints on phototherapy services. As such, patients with other dermatological diseases (such as eczema or psoriasis) who usually require shorter courses are prioritised instead. On the other hand, patients, who are undergoing phototherapy need to attend hospital 2-3 times a week for 9-12 months, which can be a major inconvenience to patients due to work, family or school commitments; therefore, phototherapy will not be applicable or relevant to all patients. Other, third line, treatments such as depigmentation and excimer laser, are only suitable to a small subset of patients. This means that these third line treatments would not be applicable to over 90% of patients with vitiligo, as they would be contraindicated to them. Current clinical recommendations for the management of vitiligo are based on trials of poor to moderate quality. Due to the lack of licensed treatments for vitiligo, and the fact that usually first line treatment for vitiligo includes topical preparations (TCS or TCI), ruxolitinib would fit into the first line treatment

	category alongside TCS and TCI and perhaps following a short trial of TCS or TCI. It is important to offer to patients with vitiligo, the most effective (as per clinical trials) and licensed treatment for vitiligo as soon as possible and preferably early on, to ensure that we (clinicians) do not miss this "window" of opportunity to treat vitiligo as soon as possible, as there is some preliminary evidence that the earlier you treat vitiligo, the better the results are.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	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. No additional investment would be needed.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes, absolutely. It is important to note that although vitiligo does not affect length of life (same most of dermatological diseases), it affects patients' mental health and quality of life. Several studies (including UK) have shown this. Based on the phase 3 trials, the results are satisfactory and were meaningful to patients and clinicians (based on VNS and VASI outcome measures, respectively).
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No

15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	I believe it will be easier to use this new cream (which could be prescribed by a dermatologist following 1 **hospital appointment**) as opposed to asking patients to attend phototherapy (in dermatology dept), which is 1) only available in a few NHS hospital (hence patient needs to travel out of area); 2) patients have to wait for over a year to initiate phototherapy due to long waiting list and 3) once commenced phototherapy, patient needs to attend 2-3 times a week for 9-12 months, i.e. 108 to 144 **hospital appointments.**
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No additional testing, however, diagnosis of vitiligo should be confirmed by a dermatologist before initiation of Ruxolitinib cream. This is because, a recent international study suggested that around 50% of patients with vitiligo were initially misdiagnosed.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	A recent retrospective, observational study using UK general practice data (2004–2020) revealed that people with vitiligo have a higher incidence of recurrent depressive disorder (RDD) and anxiety disorder compared with control groups. In addition, people with vitiligo and psychological comorbidity had more primary care encounters, more time off from work and higher unemployment (Thompson *et al.* https://doi.org/10.1192/bjo.2022.591). Finally, some quality-of-life measures may not adequately capture the impact of living with skin condition such as vitiligo, as skin in patients with vitiligo is not usually sore or painful (unless sunburned). In addition, they may not capture anxiety and depression, hence patients with vitiligo often "score" lower in these measures compared with patients with other health and skin conditions. Finally, burden of treatment e.g. phototherapy (as mentioned in Question 15) needs to be considered.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial	Yes, this is the first ever licensed treatment for this condition. The cream also showed to have good results in the trials.

impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	It is time for an effective and licensed treatment for this neglected and psychologically devastating disease.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	As per trials results, the side effects were minor, which goes in line with other topical treatments for other dermatological diseases including vitiligo.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes Internationally agreed consensus on core outcomes set for vitiligo clinical trials include: repigmentation, side effects, maintenance of gained repigmentation, cosmetic acceptability of results (measured by the Vitiligo Noticeability Scale), quality of life, cessation of spreading and tolerability or burden of treatment (Eleftheriadou *et al.* https://onlinelibrary.wiley.com/doi/abs/10.1111/pcmr.12354); therefore, the choice of outcomes in Ruxolitinib trials were appropriate.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	N/A there is no real-world data exist.
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of	This treatment should be offered to any patient with vitiligo, who wishes to treat their skin, including children over 12 years of age. Vitiligo affects any age, sex and skin type.

people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- There is currently an unmet need for licensed and effective treatment option for vitiligo, which would be easily accessible for those, who wish to treat their vitiligo.
- Phototherapy is available at a few NHS hospitals only and brings a significant burden (of treatment) when offered to patients (i.e. over 100 hospital appointments)
- Third line, treatments such as depigmentation and excimer laser, are only suitable and/or indicated to a small subset of patients (i.e. around 10%).
- This treatment should be offered to any patient with vitiligo, who wishes to treat their skin, including children over 12 years of age.
- 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.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

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Patient expert statement

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **<insert deadline>.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

Patient expert statement

Part 1: Living with this condition or caring for a patient with vitiligo

Table 1 About you, vitiligo, current treatments and equality

1. Your name	Emma Rush
2. Are you (please tick all that apply)	☒ A patient with vitiligo? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with vitiligo? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Vitiligo Support UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference

	☒ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with vitiligo? **If you are a carer (for someone with vitiligo) please share your experience of caring for them**	My experience of living with vitiligo is that it has a profound, deleterious and far-reaching impact on many aspects of my life. I first noticed a patch on my back in 1998, before I was married. It was small and invisible to almost everyone who I encountered. But it grew. It grew without me being able to control it, in places where it was very visible to every single person I met, and so it became an integral part of those encounters. We all ask questions before we meet someone new, “Will we get on?”, “Will they like me?” “Will I get the response I need?”. With vitiligo, the answers to those questions come **through** your skin disease and it becomes the third party in any social transaction that you have. New questions are now added, “Will they notice it?” (hard not to when your face has large white areas around your mouth and eyes that you’ve tried ineptly to conceal) “Will they say something” (will it be the rude and blunt or, sometimes worse, the faux empathetic comment that I receive?) “Will they not want to touch my hands?” (yes, that is an ignorant “thing” that happens), “Will they stare/point/snigger/comment to their friends in front of me” (yes, these all happen, a lot, and have to be managed in your social life). You know that sometimes you feel up, and every social transaction brings a joy, and you have days when you feel lower and you get through those transactions without engaging. Vitiligo changes every social transaction that you have. The energy you have for each transaction is partly deflected into the issue of asking yourself if they’ve noticed, will they say something, etc., which is fine when you feel up and can manage that on top of the day-to-day routine, but hard if other things in life weigh on you. I was in a relationship when my vitiligo began to grow, so there are even more questions for those who are single, relating to your vitiligo on your genitalia, on your body, and they form a barrier, the patches and the consciousness of the patches to most forms of intimacy from close friendships to sexual partners.

	I have vitiligo. It has changed my life more deeply and painfully than the other multiple chronic conditions that I have. Like most humans, I am a social being but now I shy from meeting new people. Like most humans, I used to stretch out in the sun enjoying it warming my bones, but now I avoid the burning that the sun brings. I tried camouflage, laughing a little bitterly at the name it was given, that I should be disguising myself as “normal” when I really wasn’t. I found it impossible, wearing it made me feel like I had a mask on, and I remember the embarrassment of passing it to other people on their clothes when you gave them a hug. And where do you put it when you have patches on your entire body? Which bit gets included, which bit missed out? Gradually all the colour has departed from my face, and I am white all over. Now my challenge is to find a make up that brings life to the deathly white face that I have. Small challenges, I feel you thinking, but I live in 2023, in a culture that has changed quite dramatically even from that of 2000. This is a fact that has never been accommodated in the NHS in the general mental health support it offers, let alone in a specialised subject like vitiligo. Our culture is a visual-dominated, image-centric culture. From dating apps to Instagram, people share pictures of themselves, endless selfies, pictures with your friends, family, enjoying life and looking out from the frame of the image with perfect skin. People with vitiligo do not share that joy in the imagery of their lives. I do not share that joy in the imagery of my life. My skin sets me apart from the normal, and its whiteness makes me a shadow of my former sociable self. In the dark, in parties that are low-lit, our skin glows faintly and you can see the skull beneath our skin. And I sense you reading this and thinking “That’s not painful” or “That’s something you can just make up and makeover”. But that disavows all of our psychologically painful experience. This disease changes you physically and psychologically. The way that you saw yourself, the person you were, this disease takes that away from you. You can work on those feelings (probably not with specialist help from the NHS due to cost…) and you can make a different life that accommodates how you feel about your very self, but this disease robs you of you.

	No, you're right, if that is the crude measure of effect, we are not in pain. We don't bleed. We aren't at risk of death. But the very way that we move in this intensely extroverted social world that we live in has been changed without our choice, and goes on changing, quixotically and uncontrollably. Most people resist change, particularly in the way they look. We have to submit to change, with patches appearing sometimes overnight. Women in particular are bombarded with subliminal messages about changes to their skin reflecting their age, and we have a pernicious culture of the celebration of vigorous health and dismissal of the different. Every day, we endure the clear message on our faces, hands, arms, legs, bodies, that we are changing without any control and that our skin now shows us as someone who is different, who has a disease, is no longer healthy, but is slowly being consumed by vitiligo. This is a skin disease. I know from my work running a patient support group that it can have a deep impact on people's lives. I know from my own life that it changes you, dramatically, visibly, without your choice and you have to work daily to accommodate its presence. The treatments available are time-consuming and seldom very successful. We want our disease to be accounted for with the impact that it has and to be given a treatment that treats the disease that we have. Please listen to us.
7a. What do you think of the current treatments and care available for vitiligo on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	This is the case in the UK: primary care clinicians, for the most part, triage patients out of any treatment by telling them their condition is "only cosmetic". This is entirely incorrect, and should be corrected by, inter alia, the Primary Care Dermatology Society, as a matter of some urgency. There also needs to be significantly improved education of GPs in dermatology generally but specifically in managing patients with skin diseases as trivialising them is completely unprofessional and entirely inappropriate. However, the current treatments for vitiligo are not licensed specifically for it, and they are either topical (usually the first stage of treatment) or involve narrowband

	uvb treatment (second stage only available through secondary care, where very long waiting lists exist and vitiligo is again given a very low priority). There are side effects of long term use of topical steroids, the first line of treatment, and its use in vitiligo is to mediate the autoimmune inflammatory response in the skin. Patients are never advised correctly about the use and the need for uvb light to stimulate repigmentation. There is also a calcineurin inhibitor available topically, which again is designed to reduce inflammatory responses in skin cells. Repigmentation requires some form of UV stimulus to fully occur. This particular cream is available via primary care but many GPs are not aware of this and then clog the dermatology wait lists sending patients to get a prescription for it. Narrowband uvb treatment (phototherapy) is the most effective treatment for vitiligo currently. It is only available via an appointment with a dermatologist in secondary care. This is very hard to obtain if you have vitiligo, as most GPs seem to have as their mission the dismissal of people with vitiligo back into the general public, probably feeling worse about their skin condition and certainly thinking that treating a dermatology condition is not of interest to the NHS. This also means, I believe, that numbers for vitiligo are under-reported in the UK. The downside of phototherapy is the inconvenience and cost. Vitiligo requires a year's worth of appointments and visits two or three times a week. This impacts on all aspects of a patient's life. I run a patient support group for patients with vitiligo. Currently, patients report only limited success with topical treatments and more success, but time-limited in its effect, with phototherapy. The inconvenience of phototherapy puts people off.
8. If there are disadvantages for patients of current NHS treatments for vitiligo (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Phototherapy: Adverse events/side effects: burning (above required erythema); itching; hypopigmentation; long term increased risk of skin cancers (melanoma; in particular, keratinocyte cancers).

Patient expert statement

	Disadvantages: time required; cost of travel/parking, etc.; managing skin discomfort; managing expectations as some areas repigment and others don't on each individual. Steroid cream: Side effects: long term use brings skin thinning; combating steroid phobia. Disadvantages: limited effect as not primarily licensed to treat vitiligo; should not be used for the face but is prescribed by some not particularly well-read GPs. Calcineurin inhibitors: Side effects: skin burning with alcohol intake; itch; this is generally prescribed in ointment form so Disadvantages: more effective than a steroid cream but still of limited effect as not primarily licensed to treat vitiligo.
9a. If there are advantages of ruxolitinib cream over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does ruxolitinib cream help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	a) To get pigment back on my face would be a transformation for me. I cannot tell you how much I long to see myself again. It would improve enormously my quality of life. A topical treatment that actually was devised and researched for the underlying mechanism of our disease would be such an enormous step forward. Its results are far better for repigmentation than current treatments. I am concerned that reports of its side effects relate primarily to the use of the "inib" class of drugs taken orally for systemic inflammatory disease. I think that the risk of acne is slightly off-putting but this is combined with its success in repigmenting, so is an individual choice for each patient and their clinician. Currently, side effects exist with all treatments Using a cream at home allows patients more convenience in treatment compared to the current best treatment, phototherapy. The success rates of ruxolitinib mean that it is far in advance of any current treatment on offer to patients.

10. If there are disadvantages of ruxolitinib cream over current treatments on the NHS please describe these. For example, are there any risks with ruxolitinib cream? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from ruxolitinib cream or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	I consider patients who have the added impact of cultural difficulties inherent in changes to skin colour should be a high priority for consideration for treatment. Otherwise, many, many patients wait very eagerly for a decision that will bring them hope.
12. Are there any potential equality issues that should be taken into account when considering vitiligo and ruxolitinib cream? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	I cannot think of any equality issues relating to this treatment. I would note here that patients generally now have to be sophisticated and knowledgeable advocates for their health in general. This applies in excess for patients with vitiligo who must navigate the ill-informed barriers of primary care to even access dermatology. Please make a quantitative decision, and set aside any qualitative issues that you bring to this question. Please make this decision on the basis of this being the best possible care for the greatest number of people.

13. Are there any other issues that you would like the committee to consider?	I have devoted a large portion of my life to supporting patients with vitiligo, in times of their absolute despair, in moments when their child has been diagnosed and they are overwhelmed with fear of the disease's impact on them as they grow up, when they are getting married and feel the pinch of worry at how they will look, navigating relationships, bearing friendships that let them down, tolerating comments, worrying about work. This disease casts deep roots into your very being. Yes, wouldn't it be wonderful if we all looked like Winnie Harlow and could stretch ourselves out on a billionaire's yacht and make money from our vitiligo. I'm glad she exists but we don't look like that on a daily basis. We live ordinary lives where people stare at us. We can see ruxolitinib cream as a treatment that has worked for patients in the US, is working now for patients in Europe. We only ask for a chance to treat our skin condition with something that is designed to combat it, with a fine weapon to vitiligo's heart, not just a rock to the disease's head. My responses here have been emotional, but this disease exists across the population. Not everyone will want to treat, not everyone will consider it necessary. But oh, for those who do, the need is great. Please provide us with a clinical treatment that is straightforward and that actually, finally works for our vitiligo.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

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Patient expert statement

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with vitiligo

Table 1 About you, vitiligo, current treatments and equality

1. Your name	Pawan Korpal
2. Are you (please tick all that apply)	x☐ A patient with vitiligo? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with vitiligo? x☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Vitiligo Support UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) x☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement x☐ I agree with it and **will be** completing ☐
5. How did you gather the information included in your statement? (please tick all that apply)	x☐ I am drawing from personal experience x☐ I have other relevant knowledge or experience (for example, I ☐am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference

	x☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference x☐ I have not completed part 2 of the statement
6. What is your experience of living with vitiligo? **If you are a carer (for someone with vitiligo) please share your experience of caring for them**	I got my first white patches around the age of 8, predominantly on my legs / elbows, I am now 51. I am Indian, therefore vitiligo has a huge social stigma for those many individuals like me with brown / darker skin with little to no chance of an 'arranged / introductory marriage' and other social exclusion. At school it was not possible to hide my vitiligo when doing sports. I was nicknamed 'Piggie' when the bullies were being nice. I was called 'Pigsh-t' when they were being nasty. At a very young age, my experience included being laughed at & shamed for having these white patches. This resulted in me having fights against the bullies. This never stopped the verbal bullying & shaming but did lessen it. As an adult, I find it painful that violence entered my life at such a young age and the experience of real prejudice all because my melanocytes had been 'switched off'. The psychological effect on me was profound. I pray and hope that no other child has to endure any of what I did but I know this still continues primarily due to a lack of a reliable and proven treatment and the way society treats those that are 'different'. I was fortunate that my vitiligo did not worsen for many years, and I was able to keep it covered most of the time. I was always asked by everyone when it was really hot and sunny why I was not wearing shorts, and I always made an excuse. As I became interested in girls, I was always embarrassed and shy around undressing, often making sure that any closeness was when it was dark and keeping the lights off. Around the age of 16, I visited a tattooist to see if they could apply ink that was a similar colour to my skin, they agreed to only try a small area. Around 17, I got my first patches on my face, on my eyelid and below my lip, which I later learned are classic starting places for vitiligo on the face, leading to the so-called "panda" face. I felt new negativity about my vitiligo and its effect on me, so I sought out a cosmetic

	surgeon who cut my skin and sewed it back so as to hide the patch leaving me with a faint scar. Little did I know, because accurate information was and is still scarce about vitiligo, that the face is actually an easily treatable area. These were very poor choices for a young person severely affected, mainly psychologically, by this disease, but like many people with vitiligo, I was desperate and made the decision that I thought would help with my skin disease. The above evidence is clear, this is not just a cosmetic disease, it affects every part of our psyche, our confidence, our relationships with others and ourselves. It leads to feelings of depression, to us reducing our lives to manage it's impact, and the lack of effective treatment within the NHS drives patients to seek alternatives that can be unsafe and cause skin damage, like my permanent scar. At 18, I went to India and obtained a 'treatment' from a village doctor. I was told this was snakes blood mixed with a few things. This made parts of my skin blister which would pop and liquid would ooze out. I walked around like I was walking on eggshells so as to not pop any blisters accidentally. I eventually found my way to a dermatologist, Dr Janeja (as I recall). He prescribed me psoralen tablets to combine with sun exposure and back in the UK I purchased a sunbed, yes the old dangerous type. I cannot reconcile the statement that this is just a 'cosmetic disease' with my own experiences, which I know are not unique. For many years I then used various corticosteroids topically even though they are not formally approved for vitiligo. I had constant worry around thinning skin. These did not help to improve the patches although they did seem to stop any progression in my particular case, I know that others have not had the same experience both personally and through my membership of the Vitiligo Support group. In my early 30's, I came across Professor Schallreuter, a dermatologist in Germany who took groups of patients to the Dead Sea to bathe in the healing waters and unique UVB sun rays (lowest point on earth). This was a three week trip with other vitiligo patients from around the world. She had designed a cream to apply that

	accelerated the treatment. I spoke with the Professor at every opportunity that I got about her research and future hopes. I started to gain pigment back after 13 days and made significant gains, as did many others. When I returned home to the UK, I purchased a NBUVB panel for use at home. This has been the mainstay of my treatment combining it with another treatment e.g. a cream. This also stabilised my vitiligo. I had some very good gains, however, I still had many white patches. After nearly 30 years of living with this disease, it still affects me psychologically and socially. I have travelled the earth and spent huge sums to treat this disease and I know that I have been fortunate to be able to do this and I know that many others won't have that chance and so their feelings must be worse, not having any sense of controlling their disease, and having to manage the changes in their skin, often outside the support of the NHS. I managed this through various jobs as my mum could not afford it after my dad passed away. I was pushed into making different financial choices as a young person. Don't tell me it's just a 'cosmetic disease'. I cannot go to the Dead Sea every year. It is much harder to get any repigmentation using Protopic or even Betnovate now. I need something much stronger like the steroid cream Clobetasol which carries its own risks of thinning skin. I am now at a stage of what I call 'management', knowing that repigmentation is a somewhat distant goal for me under the current treatments offered. At present, I use Clobetasol (the strongest corticosteroid and which can cause thinning skin) along with my NBUVB. I was initially 'aggressive' with its use and have now reduced this down. I use the cream twice per week with 5 days off to minimise its risks. I also have time off altogether and experiment how long I can go before I see losses. I tried 3 months which was too long. My last break after continuing was 2 weeks off and back to 2 times pw. I combine this with various supplements and antioxidants. I perhaps make 1% gains in pigment each year.

	I have achieved approx, 70% repigmentation using various methods none of which are formally approved for vitiligo apart from the NBUVB. In fact, I am a 'good responder' to the treatments. I am sure that if I had the chance to use Ruxolitinib, which has the mechanism of action of stopping the immune response at source then I would be largely able to eradicate the patches. I cannot tell you what a difference this would make to my life, to the effort spent daily managing my skin, and to the impact that vitiligo has on me, as an Indian man.
7a. What do you think of the current treatments and care available for vitiligo on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	My GP was brutally honest when I emailed the treatment guidelines for treating Vitiligo by the British Association of Dermatologists and when I suggested what I needed. He said he had no knowledge / experience and was happy to be guided by me and to follow the guidelines. Betnovate didn't work for me so we opted for Clobetasol combined with my home NBUVB panel. It is clear from Vitiligo Support UK that many patients have been 'fobbed off' by their GP's who have shown a lack of understanding of the treatment guidelines and the QOL effect of living with vitiligo, particularly the psychological effects. It is like being hurt twice for them. None of the available treatments are specifically for vitiligo, they are 'off-label'. Getting NBUVB is virtually impossible for many and the waiting times are unduly long. I have had NBUVB via the NHS but this was many years ago and IO knew this was to be a long term treatment (now over many years) so was able to buy my own NBUVB panel. The main problem is the risks associated with thinning skin and limited availability of phototherapy via the NHS, for which you have to first wait and get and

	appointment with a dermatologist. Many people do not experience positive effects using Protopic, Betnovate or Clobetasol.
8. If there are disadvantages for patients of current NHS treatments for vitiligo (for example, how they are given or taken, side effects of treatment, and any others) please describe these	NBUVB: This is very time consuming. The costs involved in travel, time away from work/education etc. The treatment seems to work in some areas and not others. This treatment does not get to the root cause of vitiligo and stop the cellular inflammatory response. Corticosteroids and Protopic: Work for some and not others. Does not get to the root cause. Thinning skin. Itching / burning sensation. Lifelong costs in managing the disease using current treatments which are hit and miss.
9a. If there are advantages of ruxolitinib cream over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does ruxolitinib cream help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	Ruxolitinib stops the mechanism of action at source. It is proven through various trials to be highly effective and more effective than current limited range available via 'off-label' treatments which still have a cost with a much lower cost / benefit ratio. This will undoubtedly improve the QOL for vitiligo sufferers. The QOL is the most important. To have less psychological effect by reducing / eliminating patches via an effective / proven treatment. I believe that Ruxolitinib would save the NHS cost overall. All of the steroids etc could be done away with, saving significant sums for current treatments which yield little cost / benefit ratio. Time would be saved from the present place of trying one cream then another and another.
10. If there are disadvantages of ruxolitinib cream over current treatments on the NHS please describe these.	Almost everything in life has a risk of some kind. The stated side effects are minimal and manageable.

Patient expert statement

For example, are there any risks with ruxolitinib cream? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from ruxolitinib cream or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Those with darker skin will most likely benefit more as the disease is more pronounced with them.
12. Are there any potential equality issues that should be taken into account when considering vitiligo and ruxolitinib cream? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	Yes. The American medical authorities have approved it for their citizens. The European medical authorities have also approved it. Both after careful reviews. I would not feel like an equal human being if the UK medical authorities (NICE) were to decline its general approval whereas other nations have. Those with darker skin where the disease is far more visible are particularly more disadvantaged. It is much harder for them to hide or try and camouflage it. Their cultures / societies also tend to outcast them.
13. Are there any other issues that you would like the committee to consider?	Shortly prior to meeting Professor Schallreuter approx 18 years ago and since then, I have absorbed as much knowledge as I can glean mainly online. I have followed the World Vitiligo Day presentations where researchers and dermatologists share

	their findings. I have followed the Ruxolitinib, other JAK inhibitors and other trials for the latest news. I have read and watched almost every word spoken / written from Dr John Harris who is at the forefront of further treatments / research as well as other dermatologists leading the field. I have communicated online directly with hundreds of other sufferers and shared my opinions, knowledge, experiences and hopes around Ruxolitinib, other treatments / research and current treatments.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- The psychological effects are unimaginable for all ages, races and gender. It is worse when you are young and are still navigating the world and your own emotions.
- Current treatments are off-label, for many they are ineffective and the cost/benefit ratio is low.
- There are many off-label treatment options. There are many different creams, steroids etc. It is trial and error as to what works for some and others. One known and effective treatment just makes economic and physical sense.
- I would like you to understand that this disease has far reaching implications for people's well being and their physical and mental health. It is a skin disease that has been a poor relation, but researchers have respected patients' experience and produced this cream. It would transform the lives of many many people.
- I feel like that I have been prejudiced and at a disadvantage all my life due to vitiligo

Thank you for your time.

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

A Single Technology Appraisal

Produced by

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Author Contributions:	
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Sophie Robinson	Critical appraisal of the company's literature search strategies and conducted additional literature searches as part the EAG appraisal
Alex Allen	Critical appraisal of the company's clinical effectiveness evidence and drafted sections of the report
Viktoria Eleftheriadou	Expert clinical advice to the EAG about NS vitiligo and its treatment
G.J. Melendez-Torres	Critical appraisal of the company submission, writing and editorial input
Caroline Farmer	Project lead, critical appraisal of the company submission, writing and editorial input

Table of Contents

List of key issues

List of tables

List of Figures

Abbreviations

A&E	Accident and emergency
AE	Adverse event
BAD	British Association of Dermatologists
BID	Twice daily
BNF	British National Formulary
BSA	Body surface area
BSC	Best supportive care
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical Study Report
DLQI	Dermatology life quality index
DP	Depigmentation
DSU	Decision Support Unit
EAG	External Assessment Group
EMA	European Medicines Agency
eMIT	Drugs and pharmaceutical electronic market information tool
EQ-5D	EuroQol five dimension
FA	Feasibility assessment
FS	Focal Seizures
GNX	Ganaxolone
F-BSA	Facial body surface area
F- PaGIC	Facial Patient Global Impression of Change
F-PhGVA	Facial Physician's Global Vitiligo Assessment
F-VASI	Facial Vitiligo Area Scoring Index
GP	General practitioner
HADS	Hospital Anxiety and Depression Scale
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health State utility value
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ITC	Indirect treatment comparison
ITT	Intention-to-treat
LTE	Long-term extension
MHRA	Medicines and Healthcare products Regulatory Agency
NA	Not applicable
NB-UVB	Narrowband ultraviolet B
NHS	National Health Service
NICE	National Institute for Health and Care Excellence

NMA	Network meta-analysis
NR	Not reported
OLE	Open label extension
NSV	Nonsegmental vitiligo
ONS	Office of National Statistics
OR	Odds Ratio
OWSA	One-way sensitivity analysis
PAS	Patient access scheme
PBO	Placebo
PSA	Probabilistic sensitivity analysis
QA	Quality assessment
QALY	Quality-adjusted life year
QD	Once daily
RCT	Randomised controlled trial
RPS	Repigmentation scores
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
TA	Technology Appraisal
TEAE	Treatment emergent adverse events
TCI	Topical calcineurin inhibitors
TCS	Topical corticosteroids
T-VASI	Total Vitiligo Area Scoring Index
VASI	Vitiligo Area Scoring Index
VitiQoL	Vitiligo-specific quality-of-life instrument
VNS	Vitiligo noticeability scale
VS	Versus
WTP	Willingness to pay

1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1. Overview of the EAG's key issues

A brief overview of the key issues identified by the EAG in their appraisal of the company submission (CS) is provided in Table 1. Further detail of the issues is provided in Sections 1.3, 1.4, 1.5, and 1.6.

The EAG identified a key issue relating to the decision problem of the appraisal, in that the CS did not demonstrate the clinical and cost effectiveness of ruxolitinib in comparison to the relevant comparators in the company's proposed positioning. A further key clinical issue related to the absence of a comprehensive evidence base in the CS for the target population for ruxolitinib, defined by the company as those who have not responded to topical corticosteroids and/or calcineurin inhibitors, or for whom these treatments are contraindicated. In terms of cost effectiveness issues, the EAG noted key issues with the company's model structure and use of clinical effectiveness data, and key patient utility and healthcare cost assumptions. Owing to outstanding key issues, the EAG was only able to tentatively state preferred cost-effectiveness results.

Table 1: Summary of key issues

ID	Summary of issues	Report sections
Key Issue 1	The clinical and cost effectiveness of ruxolitinib as compared to established treatment options is unknown	2.4, 4.2.4
Key Issue 2	The clinical effectiveness evidence presented by the company was not	2.4, 3.2.2.2, 4.2.3

ID	Summary of issues	Report sections
	representative of the target population and the population used in the company's economic evaluation	
Key Issue 3	Cost-effectiveness model's structural assumptions and use of clinical effectiveness data	4.2.5, 4.2.7
Key Issue 4	Approach to ruxolitinib dosing assumptions in the cost-effectiveness model	4.2.4
Key Issue 5	Approach to resource use and cost assumptions in the cost-effectiveness model	4.2.9
Key Issue 6	Approach to patient utility assumptions in the cost-effectiveness model	4.2.8
Key Issue 7	Approach to adverse event assumptions in the cost-effectiveness model	4.2.8, 4.2.9

The key differences between the company's preferred assumptions and the assumptions in the tentative EAG-preferred analyses are outlined in Table 2.

Table 2: Key differences between the company's preferred assumptions and EAG's preferred assumptions

	Company's preferred assumption	EAG preferred assumption	Report Sections
Treatment pathway resource use	Assumed that most patients in the "non-response" state (after ruxolitinib or vehicle cream discontinuation) incurred ongoing active treatment and disease management in secondary care.	Considered a comparison to vehicle cream to only be potentially relevant for an end-of-line positioning and assumed far lower ongoing active treatment and disease management costs in the "non-response" state.	1.3, 1.5, 2.4, 4.2.3, 4.2.9, 6.2.1
Patient utility	Company's multistep approach produced utility values for "maintenance" and "stable" states that were higher than age-equivalent general population estimates. The company's model categorised those achieving F-VASI50-74 repigmentation	Preferred to limit health state utility values to be no greater than age-equivalent general population estimates and corrected the inconsistency of assigning non-response utility values to patients achieving F-VASI50-74 repigmentation.	1.5, 4.2.8, 6.2.2

	Company's preferred assumption	EAG preferred assumption	Report Sections
	improvements at 24 weeks as non-responders, despite the multistep approach predicting higher utility values.		
Expected ruxolitinib dose	Assumed that the median pooled daily dose of trial drug (ruxolitinib or vehicle cream) from the pooled TRuE-V dataset represented the expected daily dose of ruxolitinib in practice.	Used the mean ruxolitinib dose estimate from TRuE-V summary data to inform dose expectations. As this mean estimate was greater than the maximum recommended dose in the product licence for ruxolitinib, the EAG presented two alternative dosing approaches: one in which the cost of mean dose was assumed; another in which the cost of the maximum recommended dose was assumed.	1.5, 4.2.4, 6.2.4

Abbreviations: EAG, External assessment Group F-VASI, facial vitiligo area scoring index; F-VASI50-74, 50% to 74% improvement from baseline in F-VASI

1.2. Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is an estimate of the extra cost of every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Improving depigmentation caused by NS vitiligo, and thereby improving health-related quality of life

Overall, the technology is modelled to affect costs by:

- Adding acquisition costs of ruxolitinib to the treatment pathway
- Offsetting downstream costs, by predicting a treatment effect in delaying and reducing time spend in "non-response", incurring treatment and disease management costs

The modelling assumptions that have the greatest effect on the ICER are:

- The number of ruxolitinib tubes required for an average treatment course
- The patient utility values assumed to be associated with each modelled health state.
- The cost of downstream treatments and secondary care, especially in relation to the positioning of ruxolitinib as reflected by the company's model.

1.3. The decision problem: summary of the EAG's key issues

The EAG identified one key issue with regard to the decision problem for this appraisal.

Key Issue 1: The clinical and cost effectiveness of ruxolitinib as compared to established treatment options is unknown

Report sections	**2.4, 4.2.4**
Description of issue and why the EAG has identified it as important	The NICE decision problem for this appraisal was to evaluate ruxolitinib in comparison with established clinical management, which the EAG understood to be other topical treatments (including TCS and TCIs), NB-UVB therapy, betamethasone in those with rapidly progressing disease, and combinations of these as indicated. The company submission, including the company's economic evaluation, was based on a comparison between ruxolitinib and vehicle cream (i.e. a placebo therapy). The EAG considered that a comparison with vehicle cream was only relevant for the end of the treatment pathway; i.e. after all other treatment options have been considered. However, the company stated that the appropriate positioning for ruxolitinib would be at the 2nd line position, between the use of TCS/TCIs and NB-UVB therapy. Clinical advice to the EAG was also that a 2nd line position would be more appropriate for ruxolitinib. However, the EAG did not consider that the CS was consistent with this positioning.
What alternative approach has the EAG suggested?	At clarification (question B1), the EAG requested that the company re-formulate their economic evaluation to represent a specific position in the treatment pathway, i.e., to compare ruxolitinib with the existing treatment options that it would displace. The company declined to do this. The EAG has been unable to resolve this issue during its appraisal.
What is the expected effect on the cost-effectiveness estimates?	In principle, if the efficacy of the control arm of the model was increased to reflect the use of active treatment options, the magnitude of QALY gain may decrease compared to the company's base-case analysis, which would cause the ICER to increase. However, since treatment options would incur additional cost, the incremental costs would be expected to decrease, which would cause the ICER to decrease. It was not possible for the EAG to comment on the likely magnitude of effect on the ICER due to the infeasibility of robust comparisons using available evidence for alternative comparators and in consideration of the broader structural issues with the company's model (Key Issue 3).
What additional evidence or analyses might help to resolve this key issue?	Fundamentally, the EAG considered that the company should have conducted a head-to-head trial to compare ruxolitinib with the alternative treatment options at its proposed positioning and did not

Report sections	2.4, 4.2.4
	accept the company's rationale for this not being necessary or appropriate. With the existing evidence base, the EAG accepted arguments from the company that estimating the effectiveness of established treatment options relative to ruxolitinib was challenging, given heterogeneity in trial design used to evaluate treatment options for ruxolitinib. The company should have performed a narrative synthesis of evidence for the different treatment options, to consider the relative effectiveness of treatment options in consideration of variation in trial design, and the EAG did not accept the company's rationale for not doing this. However, this would only provide an insight into the potential effectiveness of ruxolitinib as compared to existing treatment options and would not have provided reliable effect estimates for use in economic modelling. At this point, the EAG considered that either (a) ruxolitinib be considered as a final treatment option only, after all other treatment options had been considered [thus the company's analysis is relevant] or (b) the company's analysis should be re-submitted using a reasonable estimate of effectiveness for the relevant treatment comparator.

Abbreviations: EAG, External Assessment Group; TCIs, topical calcineurin inhibitors; TCS, topical corticosteroids

1.4. The clinical effectiveness evidence: summary of the EAG's key issues

The EAG considered that the CS lacked a comprehensive overview of the clinical effectiveness evidence for ruxolitinib. Notably, several clinical trials of ruxolitinib that appeared relevant to the decision problem were not included in the CS, and clinical effectiveness evidence from the included trials was not fully presented within the CS Document B. The company provided data for the scoped outcomes in supplementary documents, such as the Summary of Product Characteristics Report (SmPC) for ruxolitinib produced by the European Medicines Agency (EMA) and in PDF documents from their clinical trial reports. However, these data were difficult to identify from the documents and not always presented in a form that could support a transparent appraisal by the EAG during the timeframe of the EAG. Overall, the EAG considered that the CS presented by the company undermined the ability of the EAG to conduct a full appraisal of the clinical effectiveness evidence for ruxolitinib. However, during its appraisal the EAG did not identify any indication that the lack of transparency in the CS would meaningfully effect cost effectiveness estimates. The EAG therefore did not make this issue one of its key issues.

The EAG identified one key issue with the clinical effectiveness evidence for ruxolitinib, which was related to the discrepancy between the evidence submitted by the EAG and their proposed target population for ruxolitinib.

Key Issue 2: The clinical effectiveness evidence presented by the company was not representative of the target population and the population used in the company's economic evaluation

Report sections	**2.4, 3.2.2.2, 4.2.3**
Description of issue and why the EAG has identified it as important	The company suggested that ruxolitinib should be positioned as a 2nd line treatment option, to be considered after TCS and TCIs. However, the clinical effectiveness evidence presented in the CS was based on the full trial populations, only 28% of whom had previously received TCS or TCI treatment. The EAG was uncertain whether clinical outcomes would be expected to differ according to the line of treatment received. In response to clarification (question A2), the company provided a series of documents containing tables with clinical data for the previously treated subgroup. The files were inadequately labelled and the format of the data prevented a thorough appraisal by the EAG within the timeline available, however the EAG noted a slightly higher response rate to ruxolitinib in those who had previously received treatment compared to the full trial population, as assessed using the F-VASI75. As the EAG had not received a full submission for this population (including population characteristics including the prevalence of effect modifiers) and could not compare this finding across outcomes, the EAG was unsure if this was evidence of a true difference in treatment effect between treatment lines. Clinical data from the previously treated subgroup (any previous treatment) were used in the company's economic model, but without a comprehensive and transparent submission of evidence for the previously treated subgroup, the EAG cannot validate if the use of these clinical data was appropriate.
What alternative approach has the EAG suggested?	At clarification (QA2), the company were invited to provide evidence for the prior treated subgroup, however this was submitted in a format that could not be appraised during the timeframe of the EAG appraisal. The EAG was unable to resolve this issue during its appraisal.
What is the expected effect on the cost-effectiveness estimates?	Since this was a fundamental issue concerning the scope of the appraisal, it was not possible for the EAG to comment on the potential effect on cost-effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	To inform committee decision-making, the company should submit clinical effectiveness evidence for the previously treated subgroup in a transparent manner using the Document B template as a guide. This should include population and intervention characteristics for the subgroup (i.e., to demonstrate that clinical effects used in the model were reliable) and clinical outcome data for the subgroup across all scoped outcomes (to demonstrate if outcomes vary between the previously treated subgroup and the full population, and to validate the choice of clinical inputs used in the economic model).

Abbreviations: EAG, External Assessment Group F-VASI, facial vitiligo area scoring index; F-VASI75, 75% improvement from baseline in F-VASI; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids

1.5. The cost effectiveness evidence: summary of the EAG's key issues

The EAG identified five key issues with the cost effectiveness evidence for ruxolitinib submitted by the company.

Key Issue 3: Cost-effectiveness model's structural assumptions and use of clinical effectiveness data

Report sections	**4.2.5, 4.2.7**
Description of issue and why the EAG has identified it as important	The company's chosen model structure assumed that patients who achieve F-VASI50-74 at ~24 weeks discontinue treatment owing to non-response. This is neither in line with expectations for clinical practice nor in line with the company's own registrational trials. Separately, the company has made questionable structural economic assumptions in the model. For example, it is structurally impossible in the company's model for a patient in the "Maintenance period" state with F-VASI75-89 to achieve F-VASI≥90 and therefore transition to the model's "Stable" state. Overall, the EAG considered the company's method to incorporate data from the TRuE-V trials into the model to be subject to substantial limitations. Ultimately, this meant that the EAG had little confidence in the results of the model.
What alternative approach has the EAG suggested?	The EAG-corrected company base case (Section 6.1) corrects for a calculation error in the company's model. Other structural corrections and re-specifications were not feasible during the timeframe of the EAG's appraisal but the EAG considered these to be important for robust decision-making.
What is the expected effect on the cost-effectiveness estimates?	The combined effect of correcting for structural errors and exploring structural assumptions and the use of data that better fit expected clinical practice is unclear. While these issues are outstanding, the EAG was unable to present more than tentative EAG-preferred results.
What additional evidence or analyses might help to resolve this key issue?	The company can address this issue by addressing the structural problems identified by the EAG and documented in Section 4.2.5, and otherwise respecify the model structure to reflect expected clinical practice in line with the EAG critique (Sections 4.2.5 and 4.2.7)

Abbreviations: EAG, External Assessment Group

Key Issue 4: Approach to ruxolitinib dosing assumptions in the cost-effectiveness model

Report sections	**4.2.4**
Description of issue and why the EAG has identified it as important	The company's analysis assumed that the median daily dose of trial drug (ruxolitinib or vehicle cream) from the pooled TRuE-V dataset was equivalent to the expected daily dose of ruxolitinib in practice. However, it would have been more appropriate to use the mean dose of ruxolitinib, rather than the median dose across arms. Moreover, as the TRuE-V dosing data were skewed to the right, the mean dose of ruxolitinib in the TRuE-V dataset was greater than the median and greater than the dose limit of two 100mg tubes per month specified in the product licence for ruxolitinib[1]. This was important as the expected

Report sections	4.2.4
	per-patient use (cost) of ruxolitinib was uncertain and a key driver of cost-effectiveness results.
What alternative approach has the EAG suggested?	The EAG used a mean ruxolitinib dose estimate from TRuE-V summary data provided by the company in response to clarification question B10 to inform dose expectations in its preferred analyses. As this mean estimate was greater than the maximum recommended dose in the product licence for ruxolitinib, the EAG presented two alternative dosing approaches: one in which the cost of mean dose was assumed, another in which the cost of maximum recommended dose was assumed. The difference between these approaches was the difference between EAG-preferred tentative base cases 1 and 2 (Section 6.3).
What is the expected effect on the cost-effectiveness estimates?	Using the mean TRuE-V ruxolitinib dose (or maximum recommended dose) as a proxy for the expected ruxolitinib dose increased the expected cost of ruxolitinib and increased the EAG-corrected company base case ICER by £82,412 (£58,260), as shown in Section 6.2.7.
What additional evidence or analyses might help to resolve this key issue?	Further TRuE-V dosing data beyond the summary data provided by the company in response to clarification question B10 would further clarify doses received across participants in the TRuE-V trials. Clinical and patient expert opinion on expected ruxolitinib use in in the NHS and the likelihood of the licenced maximum dose being exceeded would help build understanding of expected doses used in practice.

Abbreviations: EAG, External Assessment Group

Key Issue 5: Approach to resource use and cost assumptions in the cost-effectiveness model

Report sections	4.2.9
Description of issue and why the EAG has identified it as important	The EAG was concerned that the company overestimated disease management and subsequent treatment resource use in its economic analysis. With respect to Key Issue 1, the EAG considered that a comparison to vehicle cream was only potentially appropriate as an end-of-line comparison. In this instance, assuming that any dermatology outpatient attendances or NB-UVB treatment after ruxolitinib or standard of care treatment (as the company do in the "non-response state") would be inappropriate. The EAG was also concerned that the company's psychological support assumptions overestimated the proportion of patients who would receive NHS psychological support. Even if the company's positioning of ruxolitinib as a 2nd line treatment option could be considered appropriate, the EAG considered that the company's NB-UVB and dermatology attendance and psychological support assumptions overestimated resource use, in a manner that biased cost-effectiveness results in favour of ruxolitinib.
What alternative approach has the EAG suggested?	The EAG removed dermatology outpatient and NB-UVB costs from "non-response" health state costs and reduced the proportion of patients expected to receive psychological support in the EAG-preferred tentative base cases. Separately, the EAG explored

Report sections	4.2.9
	scenarios assuming different levels of dermatology outpatient engagement in the "non-response" health state.
What is the expected effect on the cost-effectiveness estimates?	Compared with the EAG-corrected company's base-case results, making these adjustments caused total costs across arms to decrease and the incremental cost associated with ruxolitinib to decrease. This change in isolation causes the EAG-corrected company base case ICER to increase by £85,603, as shown in Section 6.2.7.
What additional evidence or analyses might help to resolve this key issue?	Resolution of Key Issue 1 would be the first step in clarifying appropriate resource use assumptions for patients who are in a "non-response" state after ruxolitinib and the care it would displace. Following this, further clinical expert validation of resource use frequency assumptions would help further resolve uncertainty and potential bias in the company's assumptions.

Abbreviations: EAG, External Assessment Group; ICER, incremental cost effectiveness ratio; NB-UVB, narrow-band ultraviolet B therapy; NHS, National Health Service

Key Issue 6: Approach to patient utility assumptions in the cost-effectiveness model

Report sections	4.2.8
Description of issue and why the EAG has identified it as important	The company's approach to estimate utility values for the health states in their economic model was complex and subject to numerous important limitations and assumptions. Notably, the values generated lacked face validity, implying better-than-general-population utility for patients in "Maintenance" or Stable" states. Elsewhere, the company's assignment of utility values to health states was internally inconsistent given their own estimation procedure. The company estimated a utility value of 0.890 for patients achieving F-VASI50-74 at 24 weeks. Yet, in the company's model, patients achieving F-VASI50-74 were categorised as "non-responders" and assigned a utility value of 0.797.
What alternative approach has the EAG suggested?	In EAG-preferred tentative analyses, the EAG limited health state utility assumptions to be no greater than age-adjusted general population expectations and adjusted the utility value assumed for the "non-response" state to account for the proportion of TRuE-V ruxolitinib patients expected to have achieved F-VASI50-74 at 24 weeks (assumed in the company's analysis to be "non-responders"). Separately, the EAG conducted further health state utility scenario analyses to explore the sensitivity of results to different assumptions, given the uncertainty in the estimates produced by the company.
What is the expected effect on the cost-effectiveness estimates?	Compared with the EAG-corrected company base case, applying EAG-preferred adjustments reduced the incremental QALY gain predicted for ruxolitinib. These changes in isolation caused the EAG-corrected company base case ICER to increase by £12,188 to £8,006, as shown in Section 6.2.7
What additional evidence or analyses might help to resolve this key issue?	The EAG considered that the company should have assessed HRQoL in the trials of ruxolitinib using a validated generic HRQoL measure, such as the EQ-5D, particularly given limitations in the psychometric validation of the VitiQoL measure used in the TRuE-V trials. It was not clear that the company used their systematic review to identify the best

Report sections	4.2.8
	available data to inform utility assumptions but given the TRuE-V HRQoL data collected and issues with indirect comparisons cited in the CS, there may not be substantial additional published data to further resolve uncertainty. Further patient and clinical expert testimony could help further understanding of appropriate health state utility assumptions.

Abbreviations: EAG, External Assessment Group F-VASI, facial vitiligo area scoring index; F-VASI50-74, 50% to 74% improvement from baseline in F-VASI

Key Issue 7: Approach to adverse event assumptions in the cost-effectiveness model

Report sections	4.2.8, 4.2.9
Description of issue and why the EAG has identified it as important	The company's economic analysis did not account for the HRQoL implications of adverse events, despite treatment-emergent adverse events affecting 47.7% of ruxolitinib participants in the pooled TRuE-V population, as documented in Table 23 of the CS. Treatment-arm specific expectations for adverse event costs were captured using incidence rates of adverse events occurring in ≥4% of trial participants. Though ruxolitinib was a topical treatment with no clear safety concerns in registrational trials, the EAG was concerned that the company was introducing bias in favour of ruxolitinib. The EAG's concern was heightened if ruxolitinib was considered as an end-of-line treatment (Key Issue 1), and as such would replace no treatment (no toxicity) and given the evidence from TRuE-V data that some people may expose themselves to more ruxolitinib than indicated in the product licence (Key Issue 4). Further, the EAG noted a tendency in TRuE-V trials for some patients to use more than the recommended maximum dose of ruxolitinib, which could have safety implications if such a tendency was seen in practice despite label warnings. Lastly, the company-preferred analysis predicted a modest lifetime QALY gain associated with ruxolitinib ([redacted] QALYs), while tentative EAG-preferred estimates were more modest still (~[redacted] QALYs). When incremental QALY gain estimates are of this magnitude, it was plausible that accounting for the HRQoL implications of adverse events appropriately could meaningfully affect cost-effectiveness results.
What alternative approach has the EAG suggested?	In clarification question B16, the EAG asked the company to incorporate utility and cost implications for the adverse event data in Table 24 of the CS (treatment-emergent adverse events occurring in ≥ 1% of patients in any treatment group), and in doing so to report utility, resource and cost data identification methods, and justify any assumptions required in absence of data. In response, the company did not comply with the EAG's request, or alter their CS approach to account for adverse events in the cost-effectiveness analysis in any way.
What is the expected effect on the cost-effectiveness estimates?	If vehicle cream or no active treatment was considered an appropriate comparator (Key Issue 1), appropriately accounting for the expected cost and HRQoL effects of adverse events associated with ruxolitinib would increase the expected costs and reduce the expected QALYs associated with ruxolitinib, reducing its estimated cost-effectiveness.

Report sections	4.2.8, 4.2.9
What additional evidence or analyses might help to resolve this key issue?	The company can address this key issue by complying with the EAG's request in clarification question B16; specifically, to incorporate utility and cost implications for the adverse event data in Table 24 of the CS (treatment-emergent adverse events occurring in ≥ 1% of patients in any treatment group), and in doing so to report utility, resource and cost data identification methods, and justify any assumptions required in absence of data.

Abbreviations: CS, company submission; EAG, External Assessment Group; HRQoL, health-related quality of life; QALY, quality-adjusted life year

1.6. Other key issues: summary of the EAG's views

The EAG did not identify any further key issues.

1.7. Summary of EAG's preferred assumptions and resulting ICER

Table 3 summarises the corrections and EAG-preferred changes to the company base case analysis, and their isolated and collective implications for cost-effectiveness results. As described through Sections 1.1 to 1.5, several EAG concerns remain unresolved. As such, the EAG-preferred results shown are tentative only. EAG adjustments collectively reduce the expected incremental QALY gain associated with ruxolitinib while increasing its expected incremental cost, leading to EAG-preferred tentative ICERs that were far in excess of the relevant NICE decision-making threshold range.

Table 3: Summary of EAG-preferred assumptions and tentative preferred cost-effectiveness results

Scenario	Incremental cost	Incremental QALYs	ICER (change from company base case)
Company's base case	[redacted]	[redacted]	£13,634 (+£0)
All EAG fixes to correct the company's base case applied	[redacted]	[redacted]	£13,031 (-£603)
Disable NB-UVB & vehicle cream costs, set proportion of patients receiving psychological support to 15% and proportion of patients using dermatology resources in the no response health state to 0% to represent end of treatment pathway	[redacted]	[redacted]	£100,036 (+£86,402)
Utility values capped at general population in response health states, and 'no response' utility value set to weighted average of 'no response' and F-VASI50-74	[redacted]	[redacted]	£22,639 (+£9,005)

The pooled mean over both TRuE-V studies through week 1 to week 52 exclusively for the ruxolitinib arm*	[redacted]	[redacted]	£97,359 (+£83,725)
Maximum daily dose as specified in the product licence (stating that no more than two x 100g tubes per month should be used)**	[redacted]	[redacted]	£73,000 (+£59,366)
Patients in the 'no response' health state on the ruxolitinib arm still accrue drug acquisition and disease management for a lifetime horizon	[redacted]	[redacted]	£4,114 (-£9,520)
Assume missing data are for non-responders	[redacted]	[redacted]	£16,283 (+£2,649)
EAG tentative preferred Base Case 1	[redacted]	[redacted]	£303,189 (+£289,555)
EAG tentative preferred Base Case 2	[redacted]	[redacted]	£262,880 (+£249,246)

Abbreviations: EAG, External Assessment Group; eMIT, Drugs and pharmaceutical electronic market information tool; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year
*Applicable only to EAG Base Case 1
**Applicable only to EAG Base Case 2

Modelling errors identified and corrected by the EAG are described in Section 6.1. For further details of the exploratory and sensitivity analyses done by the EAG, see Section 6.2.

2. INTRODUCTION AND BACKGROUND

2.1. Introduction

In this report, the External Assessment Group (EAG) provides a review of the evidence submitted by Incyte for the appraisal of ruxolitinib for the treatment of non-segmental vitiligo (NSV) in people aged 12 years and older.

2.2. Critique of the company's description of the underlying health problem

NSV is a depigmented skin disorder characterised by acquired, progressive, and depigmented lesions of the skin, mucosa, and hair[2]. It is believed to be caused mainly by the autoimmune loss of melanocytes from the involved areas. It is frequently associated with other autoimmune diseases, particularly autoimmune thyroid diseases including Hashimoto's thyroiditis and Graves' disease, rheumatoid arthritis, type 1 diabetes, psoriasis, pernicious anaemia, systemic lupus erythematosus, Addison's disease, and alopecia areata.

NSV is an umbrella term, which encompasses most forms of vitiligo experienced by people. The company detail the classification of NSV in Table 3 (Doc B). The two classifications notable for this submission are 'generalised or common' where patches are often symmetrical, and can affect any part of the skin, mainly hands, fingers, face, and trauma-exposed areas, and 'acro-facial' where patches affect the face, head, hands, and feet, and typically involves the perioral region and the extremities of digits.

NSV tends to spread slowly with new patches developing off and on throughout a person's life. These patches may range from specks of depigmentation through to complete depigmentation. Development of vitiligo happens through what are termed "flare-ups" and flare-ups arise from an autoimmune attack on functional melanocytes. There is no known way to predict when a person will experience a flare-up, the location of the flare-up or which patch might flare, and how far it will spread. The EAG's clinical expert stated that this unpredictable spread is distressing for the person and can lead to considerable additional depigmentation.

The EAG's clinical expert noted that 20% to 30% of people with NSV have rapidly progressing disease. This could typically a spread from 5% of a person's body surface area (BSA) to 30% of their BSA over a period of two weeks. It is difficult to capture the proportion of people

experiencing this due to NHS waiting times. People who are identified as having rapidly progressing disease use an amended treatment pathway.

Section B.1.3.1 of the company submission (CS) provided an overview of NSV. Based on advice from the EAG's clinical expert, the CS presented an accurate overview of diagnosis and classification, clinical presentation, development, epidemiology and disease burden. The company also expanded on the humanistic burden of NSV for people with the condition and their carers.

The company noted that there was currently no consensus on the methods to assess the extent of a person's vitiligo but expand upon body surface area (BSA) and Vitiligo Area Scoring Index (VASI), the methods used in the pivotal trials of ruxolitinib. The VASI method combines the extent of depigmentation with the degree of pigmentation. The EAG's clinical expert confirmed that VASI scales are accurate, however they are not widely used in practice as they are time consuming to complete.

2.3. Critique of the company's overview of current service provision

There is no NICE guideline for the management of vitiligo. In Figure 4 of the CS, the company provided an overview of the recommendations from the British Association of Dermatologists (BAD) for the management of vitiligo. The EAG considered the recommendations as reported by the company to be broadly correct, and clinical advice to the EAG was that this pathway would be followed for both young people (aged 12 and over) and adults in the NHS.

The BAD guidelines specified that the specific treatment sequence received by people with vitiligo was influenced by the progressive nature of the condition, the extent of areas affected (body surface area; BSA), the specific areas of skin affected (e.g. sensitive skin around the eyes and genitals), the level of distress experienced by the person, individual preference, and a risk-benefit profile that considers the likely risks of treatment alongside the likely benefits for the individual. This means that while the pathway in the BAD guidelines was applicable to the target population, there was likely to be variation in what treatments people would receive. However, in the main, the EAG understood that topical corticosteroids (TCS) or calcineurin inhibitors (TCIs; e.g. tacrolimus) were typically received as first-line treatment, and that people may receive both of these in sequence. If TCS and/or TCIs are not effective or not indicated, people may be considered for narrowband ultraviolet B therapy (NB-UVB) alone or in combination with either TCS or TCIs. A large UK-based trial[3] demonstrated that NB-UVB therapy in combination with

topical steroids was more effective for vitiligo than either treatment alone, however clinical advice was that NB-UVB therapy was still used more commonly than the combination treatment, though this may change with time and further dissemination of the BAD guidelines. Topical treatments may be less preferable for those whose condition has a high BSA, as would hand-held NB-UVB therapy as opposed to 'full cabinet' NB-UV therapy. Clinical advice to the EAG was that handheld NB-UVB was only available in a small number of centres in the UK, and so most people using this treatment would travel to healthcare settings to receive full cabinet NB-UVB. There were no specific management recommendations for those with vitiligo affecting the face, except that some existing treatments may not be considered appropriate for the sensitive area around the eyes. In those with rapidly progressive disease (approximately 30% of the population), people may not be administered TCS or TCIs and instead may initially be offered NB-UVB therapy. Oral betamethasone would be the second line option for those with rapidly progressive disease. Other treatments for vitiligo mentioned in the BAD guideline, such as de-pigmentation treatments and surgery, were not routinely available in the NHS.

Clinical expert advice to the EAG was that waiting times for referrals to a dermatologist may be long, and so people may receive a short course of TCS from their GP while waiting for specialist input. At that time point they may receive a longer course of TCS and/or TCIs or would be considered for other treatment options. There may be a high level of attrition within the treatment pathway, as people with vitiligo stop pursuing (further) active treatments and use maintenance strategies only, such as camouflage make-up and sunscreen. This may be particularly true for treatments such as full-cabinet NB-UVB therapy that require multiple in-person appointments, as these can be challenging to schedule alongside school and work.

Clinical advice to the EAG was that people with NSV who are experiencing psychological distress related to their condition would be encouraged to self-refer to psychological services. Self-help techniques may also be recommended for those with mild distress.

2.4. Critique of company's definition of decision problem

The population for this appraisal specified in the NICE scope was 'people aged 12 years and older with NSV with facial involvement', which was consistent with the marketing authorisation for ruxolitinib. The company proposed that treatment should be limited to people who have not responded to topical treatments (TCS or TCI) or for whom topical treatments are contraindicated, not tolerated or otherwise medically inadvisable. In principle, the EAG did not disagree with the company's proposed positioning after 1st line, and clinical advice to the EAG

was that topical treatments would still be considered before ruxolitinib as a treatment option. However, the EAG considered it plausible that the availability of another treatment in the 2nd line position may increase the number of people who choose to move beyond TCS and TCI, either to pursue further efficacy gains and/or because of concerns about the potential side effects of TCS and TCI treatment.

Consistent with their proposed positioning of ruxolitinib, between current 1st and 2nd line treatment options, the company argued that the relevant comparator for ruxolitinib was the comparator used in their clinical trials (vehicle cream, i.e. a placebo) as there was no other treatment currently in this position of the pathway. At clarification (question B1), the EAG requested that the company provide evidence to substantiate their positioning of ruxolitinib, particularly with reference to the company's argument that the comparator in their clinical trials (vehicle cream) would be the relevant comparator in its economic analyses. An overview of the response provided by the company and the EAG appraisal of this is shown in Table 4. Overall, the EAG considered that the relevant comparator for this position in the treatment pathway was existing 2nd line treatment options, which for most people with vitiligo will be NB-UVB therapy with or without TCS or TCIs. The EAG understood that those with rapidly progressing disease would not be ineligible for treatment with ruxolitinib, and so betamethasone may also be a relevant comparator at 2nd line. While clinical advice to the EAG was consistent with evidence presented by the company that many people with vitiligo were not receiving any active treatment for their condition, the EAG did not consider that this negated the need for this appraisal to determine the clinical and cost effectiveness of ruxolitinib relative to existing treatments used in the NHS. Moreover, the EAG did not consider that the company had provided evidence or rationale to conclude that the same factors influencing treatment use would not also affect ruxolitinib (and so ruxolitinib would not be a realistic treatment option for those not currently receiving treatment). However, the EAG considered that a comparison with no treatment may be a reasonable comparator to ruxolitinib in the 3rd line position in the treatment pathway, as at this point in the pathway there were no existing treatment options available (and therefore a comparison with no treatment would reflect the choice for people with vitiligo at this stage of treatment). Clinical advice to the EAG was consistent with the company's proposed positioning of ruxolitinib as a 2nd line treatment option. The EAG therefore did not disagree with the company's proposed positioning, but rather considered that the evidence base submitted by the company was not appropriate for decision-making in this position. This issue is outlined in Key Issue 1.

Table 4: Company rationale and EAG view on the positioning of ruxolitinib and consideration of vehicle cream as the principal comparator

Company response to clarification	EAG view
A retrospective cohort study amongst vitiligo patients in the UK found that among the prevalent cohort of 44,910 patients in 2019, 85.0% of patients were not on vitiligo-related treatment. In the first year after diagnosis, 60.8% of patients did not receive any vitiligo-related treatment (e.g., topical steroids, topical calcineurin inhibitors, oral steroids, phototherapy), increasing to ≥82.0% from the second year onward[4]. This finding is indicative of the vast majority of prevalent patients, including those with prior failure with TCS or TCI, not proceeding to another line of off-label therapy. In the first year, patients were recorded as having been prescribed topical corticosteroids (29.1%), topical calcineurin inhibitors (11.8%), and oral corticosteroids (4.2%). From the second year onward, the percentage of patients prescribed oral corticosteroids remained stable, while prescription of topical corticosteroids and calcineurin inhibitors declined to 11.4% and 3.9% in the second year, respectively, remaining low thereafter[4].	Consistent with the evidence presented by the company, clinical advice to the EAG was that many people with vitiligo may not be receiving treatment. Clinical advice to the EAG was that this may be due to frustration with long waiting lists to see a consultant about their condition. As ruxolitinib was expected to be prescribed by a consultant, the EAG considered it plausible that uptake of ruxolitinib would be similarly affected, and that ruxolitinib would not therefore offer an alternative treatment option for this group. Clinical advice was also that people with vitiligo may not receive treatment due to a lack of effective treatment options. The EAG assumed that this may affect treatment uptake after existing treatment options had been exhausted (i.e. after participants had not responded to 2nd line treatment options). In this context, 2nd line treatment options would still be relevant for comparison with ruxolitinib. The EAG considered it plausible that there may be people not receiving treatment for their condition because 2nd line treatment options were contraindicated, or collaborative decision-making between clinician and patient had determined that the balance of risks and benefits were not acceptable. The EAG therefore considered that the availability of ruxolitinib would encourage some people in this group to seek treatment when they would not otherwise, though the precise numbers of people this would affect are unknown. Overall, the EAG did not consider that the company had presented sufficient evidence or rationale to determine whether a group not receiving treatment would do so following the availability of ruxolitinib.
Given the availability of generic TCS and TCI, ruxolitinib cream is not anticipated to be cost-effective in the full population.	The EAG agreed that, given the widespread availability of TCS and TCIs used in the 1st line and the evidence that a significant minority of people with vitiligo respond well to these, it was likely that ruxolitinib would not be cost effective for use as a 1st line treatment for this population.
This positioning is considered most appropriate since introduction of a topical treatment after failure of initial topical treatment but prior to phototherapy is less burdensome for patients with vitiligo and less of a strain on NHS resources.	The EAG considered that the resource use associated with ruxolitinib as compared with NB-UVB therapy could be more appropriately considered within a cost effectiveness analysis comparing these treatments.
There remains a lack of equitable access to phototherapy, which is further compounded by other competing chronic inflammatory skin disease	As noted above, the EAG was aware that many people with vitiligo may not receive active therapies due to difficulties in accessing care. However, the

indications for phototherapy such as psoriasis and atopic dermatitis, resulting in long wait times and variability in receiving this treatment option across the UK	EAG did not consider that this negates the need to determine the clinical and cost effectiveness of ruxolitinib relative to available alternative treatments. Moreover, the EAG did not consider that the company had provided evidence or rationale to determine whether ruxolitinib would be used by people who were not accessing existing treatments. For example, and as noted above, the EAG understood that ruxolitinib would be prescribed by a consultant, and therefore may not be received by people who do not seek treatment from a consultant.
Clinicians generally recommend that phototherapy is prioritised for patients with large BSA (i.e., >10%) affected[5,6].	This issue raised by the company was consistent with clinical advice to the EAG that those with a larger BSA of vitiligo may find topical treatments less pragmatic, and so may prefer to receive NB-UVB (phototherapy). However, the EAG was aware that NB-UVB may be administered through the use of a hand-held device, suitable for smaller areas of the body, or 'full cabinet' NB-UVB, suitable for larger BSA of vitiligo. While clinical advice to the EAG was that there may be variable access to handheld devices in different NHS trusts, the EAG received clinical expert advice that people with a BSA <10% may still receive NB-UVB therapy. The EAG advisor noted that NB-UVB therapy could be prescribed to any person who has not responded to topical 1st line treatments and wishes to pursue a further active treatment. The EAG also noted that a requirement for >10% BSA was not specified as eligibility criteria for NB-UVB therapy in the BAD guidelines. Overall, the EAG agreed that it was plausible that there will be a group of people who would not choose to receive a topical treatment (at least as a monotherapy) if their vitiligo had a large BSA but did not consider it clear that those with a smaller BSA would not consider NB-UVB.

Source: Company clarification response (question B1)

Table 5: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Company rationale if different from the final NICE scope	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.	NA	Clinical effectiveness evidence presented by the company was consistent with the NICE scope; i.e. people aged 12 years and older with NSV and facial involvement. However, the economic analysis presented by the company was based on a sub-population of the NICE scope population, limited to people who have previously received treatment (although the choice of the comparator used in the economic analyses was inconsistent with the use of this population). In principle, the EAG did not disagree with the positioning of ruxolitinib as a 2nd line treatment option, though as noted in Key Issue 2, did not consider that the CS was consistent with this population. The EAG was unable to determine whether the clinical effectiveness of ruxolitinib varied according to treatment line. Clinical advice to the EAG was that topical treatments, including ruxolitinib, may not be appropriate for people whose condition covers a large body area. The licence for ruxolitinib limits use of ruxolitinib to be applied to less than 10% BSA. However, the EAG expected that those with a higher overall BSA may still be eligible to

	Final scope issued by NICE	Decision problem addressed in the company submission	Company rationale if different from the final NICE scope	EAG comment
				apply ruxolitinib to some of their vitiligo patches up to this BSA. Clinical advice to the EAG was that those with rapidly progressing vitiligo may be referred for NB-UVB therapy or oral treatment with betamethasone rather than for topical treatments. However, the EAG noted that those with rapidly progressing disease are not precluded from receiving ruxolitinib.
Intervention	Ruxolitinib cream	Ruxolitinib cream	NA	In the trials, ruxolitinib could be used alongside inactive management strategies, such as camouflage make-up, sunscreen and emollients. No active treatments for vitiligo were permitted during the TRuE-V trials. The EAG's clinical advisor stated that they would not consider prescribing ruxolitinib in combination with other active treatments, due to the lack of evidence for the safety of this approach. The licence for ruxolitinib[1] also advises against using ruxolitinib in combination with other topical medicinal products in the same skin areas. However, the EAG considered it plausible that some clinicians may prescribe ruxolitinib in combination with other treatments, including topical treatments used on separate body areas.
Comparator(s)	Established clinical management without ruxolitinib cream	Vehicle cream	To date, established clinical management involved the use of off-label treatments, which consist	As outlined in Key Issue 1, the EAG disagreed with the company's definition of the relevant comparator as vehicle

	Final scope issued by NICE	Decision problem addressed in the company submission	Company rationale if different from the final NICE scope	EAG comment
			of TCS, TCI, phototherapy, laser therapy, topical vitamin D analogues, and a combination of phototherapy with TCI/TCS. Ruxolitinib cream is anticipated to be positioned as a step change option between first and second line for adults and adolescents from 12 years of age with NSV with facial involvement for whom the disease has not responded to TCS, TCI, or for whom TCS or TCI are contraindicated, not tolerated or otherwise medically inadvisable. Therefore, TCS, TCI and phototherapy are not relevant comparators. Given the lack of treatment alternatives in the anticipated positioning, vehicle cream as investigated in the double-blind phase of the TRuE-V trials[7,8] is an appropriate comparator for the appraisal of ruxolitinib cream. Notwithstanding this positioning in the treatment pathway, an ITC FA was conducted to also investigate the feasibility of deriving treatment effect estimates for ruxolitinib cream relative to TCS, TCI and phototherapy. The ITC FA found that there is an insufficient evidence base to robustly compare the	cream, which was not used as a treatment for vitiligo. While in principle the EAG accepted the proposed positioning for ruxolitinib (between 1st and 2nd line), the clinical decision to use ruxolitinib would therefore be a decision between ruxolitinib and existing 2nd line treatments. The EAG therefore concluded that the relevant comparison was between ruxolitinib and existing 2nd line treatments. Several treatments used for vitiligo are not currently available within the NHS, including excimer laser therapy and skin grafting. Established clinical management was considered by the EAG to include those treatments typically used within the NHS in addition to non-active strategies, such as camouflage make-up and sunscreen.

	Final scope issued by NICE	Decision problem addressed in the company submission	Company rationale if different from the final NICE scope	EAG comment
			efficacy of ruxolitinib cream to existing off-label therapies.	
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[7] studies. However, Incyte deems that the endpoint of time to relapse (< F-VASI75) in the long-term treatment extension study (TRuE-V LTE[9]) adequately captures the maintenance of response to treatment.	NA	The company presented evidence for all of the scoped outcomes, thought agreed with the company that evidence for cessation of spread and stabilisation of vitiligo was based on the assessment of relapse rates in the TRuE-V-LTE trial.

	Final scope issued by NICE	Decision problem addressed in the company submission	Company rationale if different from the final NICE scope	EAG comment
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	NA	The company presented an economic analysis that is in keeping with the reference case. The time horizon specified is sufficient but may be considered excessive.
Subgroups	Not included in the draft scope	Due to the anticipated positioning of ruxolitinib cream, the subgroup “prior therapy” is used in the base case, and additional analyses	Vitiligo is more noticeable in people with darker skin tones and associated with higher disease burden, therefore differential cost-effectiveness is expected in this subgroup. A request was made during the decision problem	The company presented evidence according to Fitzpatrick skin type, though noted that the comparison reported was different to that the company stated was requested in the decision problem meeting (the company presented a comparison between Fitzpatrick scale Type I/II and

	Final scope issued by NICE	Decision problem addressed in the company submission	Company rationale if different from the final NICE scope	EAG comment
		are presented using the intention-to-treat (ITT) population and the subgroup "Fitzpatrick Skin Type IV-VI".	meeting that Incyte presents this subgroup analysis.	Type III/IV/V/VI). The EAG was uncertain if this analysis would fully determine whether those with the darkest skin types experience a differential treatment effect. The company suggested that this would be the case.
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	Although vitiligo is more noticeable in people with darker skin tones, as noted in the draft scope, and while we expect differential cost-effectiveness in this subgroup due to the different impact of repigmentation on HRQoL, Incyte aims to make ruxolitinib cream available for all patients. Therefore, no equality issues are foreseen in terms of providing ruxolitinib cream to eligible patients, including adults and adolescents from 12 years of age.	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

3. CLINICAL EFFECTIVENESS

3.1. Critique of the methods of review(s)

The company undertook a systematic literature review (SLR) to identify and summarise the comparative efficacy and safety of treatment options (either as independent or as combination therapy) available for people with vitiligo, including ruxolitinib cream. The search strategies, eligibility criteria, screening, data extraction, and quality assessment appeared appropriate. Overall, the EAG found the company's SLR methods to be of reasonable quality and, if followed, would likely have identified all relevant studies for the appraisal. However, the EAG conducted a simple search of the trial registers using terms for 'ruxolitinib' and 'vitiligo' and found six additional records (nine rather than the three reported in the CS). As these were all trials of ruxolitinib, the EAG was unsure why they were not identified by the company in the SLR and presented in the CS.

A summary of the EAG's critique of the methods implemented by the company to identify evidence relevant to the decision problem is presented in Table 6. The company used the results of the SLR to assess the feasibility of an indirect treatment comparison (ITC) and these methods are critiqued in section 3.4**Error! Reference source not found.**.

Table 6: Summary of EAG's critique of the methods implemented by the company to identify evidence relevant to the decision problem

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Appendix D	The search strategies were well structured and executed with a good range of sources. Terms for vitiligo were appropriately combined with terms for ruxolitinib and comparators. To this was added a broad filter for clinical trials and prospective studies. Case reports and conference abstracts were excluded and results were limited to English language only. The company carried out clinical trials searches in WHO ICTRP and in clinicaltrials.gov, the strategies used were not described. The EAG carried out trial searches in the same two sources using a simple strategy (vitiligo AND (ruxolitinib OR opzelura)) and found nine trial records in contrast to the three trials in the CS (plus a further trial mentioned in clarification). It was not possible for the EAG to appraise the additional trials within the timeframe of the appraisal, although the trials appeared to include two completed trials of ruxolitinib for the treatment of vitiligo that included clinical efficacy outcomes relevant to this appraisal.

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Inclusion criteria	Appendix D, Table 6	The eligibility criteria used in the SLR was wider than that of the Final scope issued by NICE. For example, the population included adolescents and adults diagnosed with "any type" of vitiligo, rather than limiting to people with NSV. While EAG did not consider this was a risk that relevant studies had been missed, it led to the SLR containing studies with limited applicability to the decision problem.
Screening	Appendix, D1.1.3	The EAG considered the methods for screening to be adequate.
Data extraction	Appendix, D1.1.4 and D1.1.6	The EAG was satisfied with the data extraction process.
Tool for quality assessment of included study or studies	Appendix, D1.1.9	The EAG noted that the quality assessment presented in Document B used the CRD's "minimum criteria for assessment of risk of bias in RCTs". No additional sources of potential bias were considered, and the tool was used inappropriately to assess the single arm component (Cohort B) of the TRuE-V-LTE trial. The EAG identified additional risks of bias in the key trials for ruxolitinib that were not identified by the company. All RCTs identified by the company in their SLR were assessed using the Cochrane Risk of Bias assessment (RoB 2) tool[10] and used suitable tools for the non-randomised and single-arm trials.
Evidence synthesis	SLR[11]	As noted above, the inclusion criteria led to the SLR including 253 studies, a proportion of which have limited applicability to the decision problem. The company presented outcomes from the included studies in tables that were ordered by study design and by treatment group. No meta-analysis or narrative synthesis was undertaken. The EAG accepted that a proportion of the studies had limited applicability, however evidence synthesis focusing on studies that were closely related to the decision would have supported decision-making. This could have been a narrative synthesis of studies in the NSV population where treatments relevant to the decision problem such as TCS, TCI, and NB-UVB, alone or in combination, were compared to each other or to a placebo treatment such as vehicle cream. This synthesis would have contextualised the evidence landscape surrounding the decision problem and have provided further clarity about the feasibility of an ITC.

Abbreviations: CS, Company submission; EAG, External Assessment Group; ITC, indirect treatment comparison; NSV, nonsegmental vitiligo; SLR, systematic literature review; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids.

3.2. Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1. Studies included in the clinical effectiveness review

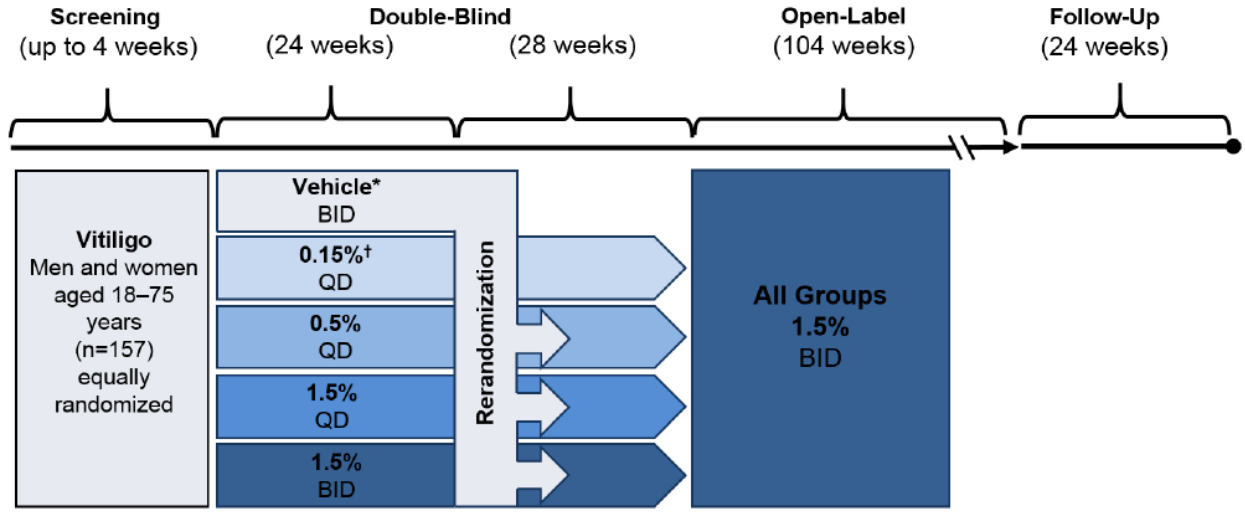
The CS described two trials: TRuE-V1[7] and TRuE-V2[8] (Table 7). These were two 'identically designed' international phase 3, double-blind, randomised controlled trials (RCTs). In each trial,

treatment with ruxolitinib was compared to vehicle cream (i.e. a placebo intervention). The trials each included a 24-week double-blind phase, after which point treatment was unblinded and participants who received vehicle cream could choose to switch to ruxolitinib up until the end of the trial (the open-label extension [OLE]; final follow-up 52 weeks). At the end of the OLE, those participants who had complied with treatment, completed sufficient outcome measures and showed no safety concerns were eligible to participate in a further trial extension (TRuE-V LTE[9]). In this trial, those who responded to treatment in the earlier trial phases entered a double-blind RCT comparing either continuation with ruxolitinib (long-term treatment) or switching to vehicle cream (withdrawal). Those who were allocated to vehicle cream in the LTE could restart ruxolitinib following relapse, and therefore the trial also provided evidence on the management of relapse. Those who did not respond to treatment during the earlier trial phases (as defined by less than 90% facial repigmentation) entered an open-label, single arm evaluation of continued ruxolitinib.

The EAG was aware that a phase II trial of ruxolitinib had also been conducted. This was identified in the company's SLR but no details of the trial or its findings were reported in the CS. This was queried by the EAG at clarification (question A15), and in response the company provided the CSR for the trial[12], though on examination the version provided by the company did not contain full data for the trial (notably, missing safety data for the double-blind phase of the trial). The company did not provide a rationale for why evidence from this trial had not been presented in the CS.

The Phase II trial was a randomised, double-blind, vehicle-controlled, dose-finding study in adult participants with vitiligo (≥0.5% of facial BSA and ≥3% of non-facial BSA). Four doses of ruxolitinib were evaluated: 0.15% QD, 0.5% QD, 1.5% QD, 1.5% BID (the latter, highest dose being the dose evaluated in the TRuE-V trials). After 24-weeks of treatment, those in the vehicle arm and those on the lowest dose (0.15% QD) who had not achieved a response were re-randomised to one of the higher dose ruxolitinib arms (still blinded). After 52 weeks from baseline, participants with no safety concerns, no clinically significant changes in laboratory parameters, and had completed sufficient assessments were invited to participate in a further 104 week open-label extension period (study design shown in Figure 1).

Figure 1: Phase II trial study design



* Rerandomization to 0.5% QD, 1.5% QD, or 1.5% BID at Week 24 for vehicle group.
† Rerandomization to 0.5% QD, 1.5% QD, or 1.5% BID if <25% improvement in F-VASI at Week 24.

BID = twice daily; F-VASI = facial Vitiligo Area Scoring Index; QD = once daily.

Source: INCB 18424-211 CSR[12]

The EAG considered that evidence from the Phase II trial should have been provided in the CS for this appraisal. Within the double-blind 52-week period, the trial could provide information about the safety of ruxolitinib (i.e. before participants with 'safety concerns' from ruxolitinib were excluded from the trial). Moreover, clinical outcomes for the 1.5% BID arm could be compared with the findings of the Phase III trials, and a comparison between dose arms could provide information about the possibility of a dose response (this issue is of relevance to this appraisal, see Section 3.2.2.3and 4.2.4). Within the timeframe of this appraisal, the EAG was unable to fully appraise the evidence from this trial.

Finally, shortly before submission of this report, the EAG identified two other Phase II trials of ruxolitinib that were not described in the CS. These were:

- TRuE-V MOA - NCT04896385 A Study to Evaluate the Mechanism of Action of Ruxolitinib Cream in Subjects With Vitiligo (TRuE-V MOA) [Completed]. Phase 2.[13]
- NCT02809976 - Topical Ruxolitinib for the Treatment of Vitiligo [Completed]. Phase 2.[14]

At the same time, the EAG also identified three additional ongoing trials not described in the CS. These were:

- NCT05750823 - A Study to Assess the Safety and Efficacy of Ruxolitinib Cream in Participants with Genital Vitiligo [Recruiting]. Phase 2.[15]
- NCT05247489 - A Study to Evaluate the Safety and Efficacy of Ruxolitinib Cream With Phototherapy in Participants With Vitiligo [Active, not recruiting].Phase 2.[16]
- NCT05872477 - Promoting Repigmentation After Epidermal Cell Suspension Grafting and preVENTing the Loss of Melanocytes Using Topical Ruxolitinib for Vitiligo in Resistant Areas (PREVENT) [Not yet recruiting]. Phase 2.[17]

The EAG was unsure why these studies were not identified by the company's SLR or discussed in the CS. The EAG was unable to fully appraise these trials during its appraisal, however identified that the first completed trial (TRuE-V MOA) was a randomised, double-blind, vehicle-controlled trial with an open-label extension that assessed safety and efficacy outcomes and may therefore have been of relevance to this appraisal. The second completed trial was potentially less relevant for consideration, as this was a small (N=11), single-arm trial.

Completed trials of ruxolitinib are shown in Table 7. Trials shown in grey are those for which the company did not provide clinical effectiveness and safety evidence in the CS.

Table 7: Completed clinical trials of ruxolitinib for the treatment for vitiligo

Study name and acronym	Study design	Population	Intervention	Comparator	Study type
TRuE-V1[18]	Double-blind RCT	Adolescents and adults aged ≥ 12 years with NSV affecting the face (≥ 0.5% BSA on the face, ≥ 0.5 F-VASI) and ≥ 3% BSA on non-facial areas, ≥ 3 T-VASI, and total body vitiligo area (facial and non-facial) not exceeding 10% BSA N=330	Ruxolitinib	Vehicle cream	Clinical efficacy and safety
TRuE-V2[19]	Double-blind RCT	As TRUE-V1 N=344	Ruxolitinib	Vehicle cream	Clinical efficacy and safety
TRuE-V LTE[9]	Double-blind RCT [Cohort A – those who responded to ruxolitinib during the previous trials] followed by an open-label extension in those who relapsed Open-label single-arm trial [Cohort B – those who did not respond to ruxolitinib during the previous trials]	Participants from TRuE-V1 and TRuE-V2 who had complied with treatment up to the final follow-up and showed no safety concerns Cohort A N = 116 Cohort B N = 342	Continuation with ruxolitinib	Discontinuation of ruxolitinib (to vehicle cream); Re-initiation of ruxolitinib following relapse	Clinical efficacy and safety
INCB 18424-211[12]	Double-blind RCT	Adults aged 18-75 years with vitiligo	Alternative doses of ruxolitinib	Vehicle cream	Dose-finding, safety

		N=157		Dose comparison	
TRUE-V MOA[13]	Double-blind RCT	Adults with NSV affecting the face (≥ 0.5% BSA on the face, ≥ 0.5 F-VASI) and ≥ 3% BSA on nonfacial areas, ≥ 3 T-VASI; total body vitiligo area (facial and nonfacial) not exceeding 50% BSA. N=60	Ruxolitinib	Vehicle cream	Clinical efficacy and safety
NCT02809976[14]	Single-arm trial	Adults with vitiligo covering at least 1% of total BSA N=11	Ruxolitinib	None	Clinical efficacy

Abbreviations: RCT, randomised controlled trial

Note: Trials that are greyed out did not form part of the CS and were not appraised by the EAG during this appraisal.

3.2.2. Description and critique of the design of the studies

3.2.2.1. Design of the studies

The two main trials for ruxolitinib presented in the CS, TRuE-V1 and TRuE-V2, used the same design: these were double-blind, randomised, placebo (vehicle cream)-controlled trials with 2:1 randomisation, followed by a single-arm, open-label extension. Randomisation was stratified by geographic region (North America vs Europe) and Fitzpatrick skin type. More than two thirds of trial centres were based in North America. No centres were based in the UK but the EAG was unaware of any rationale to suggest that this would limit the generalisability of the trial data. The EAG agreed with the company's rationale for pooling the two trials: while minor variations in participant demographics and clinical outcomes were noted between the two trials, the EAG agreed that the trials were of the same design and that pooling would provide a better representation of the clinical effectiveness of ruxolitinib.

As noted in Key Issue 1, the EAG did not consider the choice of vehicle cream as the trial comparator to be informative for determining the appropriate positioning of ruxolitinib in the treatment pathway, or for informing cost effectiveness estimates. However, the EAG considered the design to be acceptable for determining whether ruxolitinib was clinically effective as compared to no treatment.

The TRuE-V-LTE trial included two thirds (68.0%) of participants from the TRUE-V1 and TRuE-V2 trials. These were participants who completed the previous trials with good compliance and who tolerated ruxolitinib without safety concerns. The trial split participants into two cohorts depending on their response to ruxolitinib in the previous trial phases: Cohort A was comprised of participants who had an excellent response to ruxolitinib treatment by 52 weeks (as defined by 90% repigmentation, F-VASI90) and Cohort B was comprised of participants who had not shown this level of response by week 52. As participants included those who had been randomised to vehicle cream during the initial 24-weeks of the trials, the assessment of whether participants had responded to treatment was based on a timeline ranging between 28- and 52-weeks. Those in Cohort A (responders) were randomised to either continuation with ruxolitinib or discontinuation to vehicle cream (double-blind). The findings of this analysis were useful for assessing maintenance of response in those either continuing or withdrawing from treatment. Those in Cohort B (non-response or response <F-VASI90) all continued to receive open-label ruxolitinib. The findings of this analysis were useful for assessing clinical outcomes with longer treatment duration. The EAG considered the findings of the TRuE-LTE trial to provide an insight

into longer term outcomes, including whether the effect of ruxolitinib would be maintained over time (with or without continued treatment). However, as the trial was limited to a sub-sample of the original trials, the selection of which may be open to selection bias, the EAG considered that the findings should be interpreted with caution. Moreover, the EAG noted that the threshold used to determine response (F-VASI90) was higher that the threshold for a response used by the company elsewhere in the submission (F-VASI70) and supported by clinical advice to the EAG. The findings of the TRuE-V-LTE therefore had limitations in generalisability that need to be considered when interpreting the findings.

The double-blind phase of the trials had a follow-up of 24 weeks while the open-label phase was 28 weeks, thus resulting in a combined follow-up of 52 weeks. Clinical advice to the EAG suggested that the mechanism of ruxolitinib would result in a gradual response over time, which was supported by the clinical effectiveness data. Treatment response was shown to increase in a minority of participants up to the 52-week follow-up, suggesting that for the vast majority of participants, the trial follow-up was sufficient for assessing treatment response. Further follow-up of people continuing on ruxolitinib was available in the TRuE-V-LTE trial (up to 103 weeks).

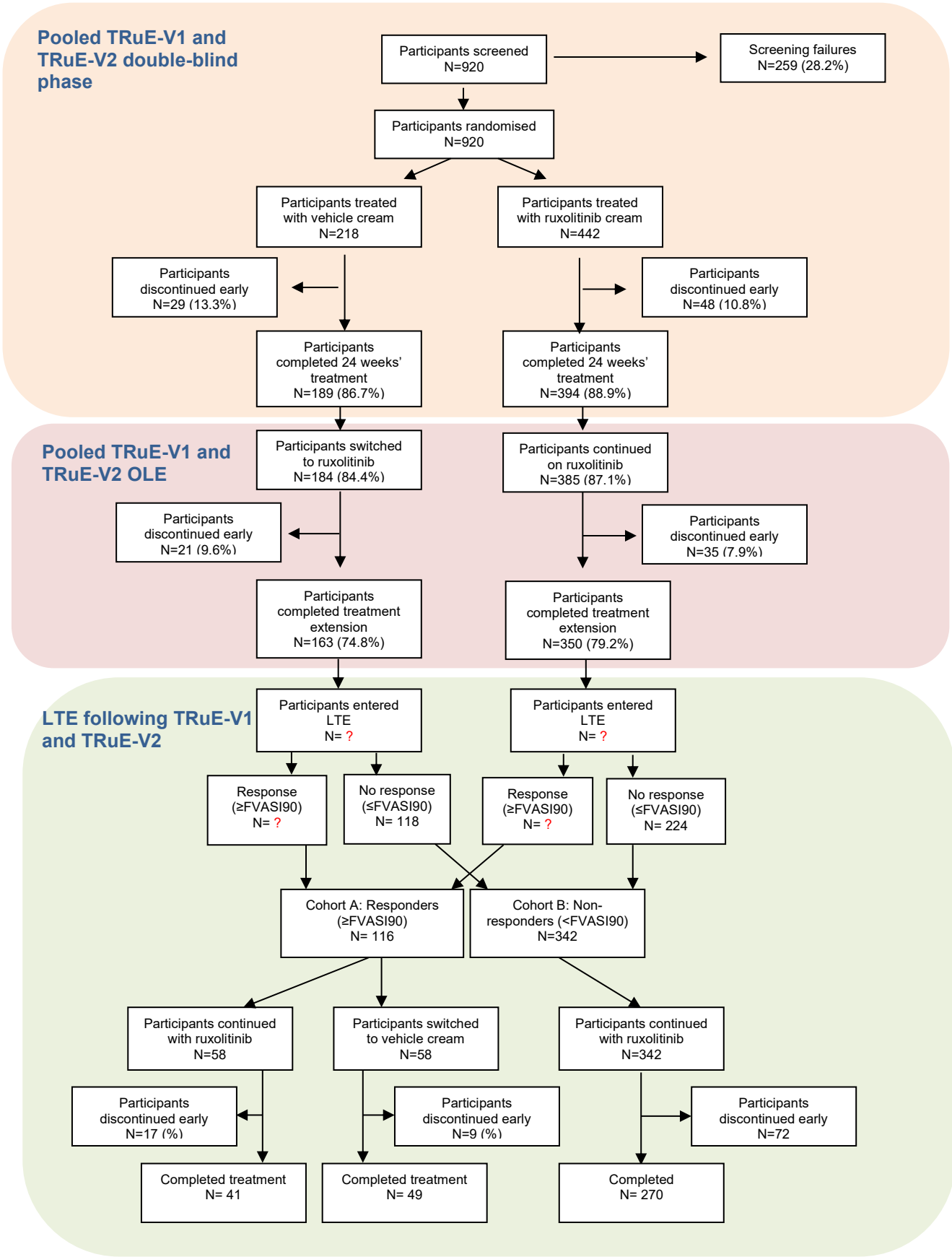
However, the EAG was less clear to what extent the length of follow-up was appropriate for determining maintenance of the treatment response. Data from the TRuE-V-LTE trial suggested that further follow-up was needed to determine the typical duration of response. The TRuE-V-LTE trial reports treatment efficacy after one round of re-treatment with ruxolitinib in those with a high level of response (F-VASI90). However, a limitation of the trials is that the efficacy of retreatment for those with a lower prior response was not captured, nor was the efficacy of multiple rounds of re-treatment. This issue is discussed further in Sections 4 and 6.

The EAG considered that the psychological impacts of change in vitiligo outcomes may take longer to demonstrate and may not be evident during the double-blind phase of the trials. However, the EAG considered that the 52-week follow-up and beyond would be a reasonable timeframe for evaluating these outcomes.

Finally, while the EAG considered that the trials were sufficiently long to capture any immediate adverse effects, the SmPC[1] for ruxolitinib noted that the trials may not be long enough to assess whether ruxolitinib was associated with any meaningful long-term risks. Specifically, as discussed in Section 3.2.3.1, the trials were unlikely to capture the risk of nonmelanoma skin cancer.

Participant flow across the different phases of the trials and their extensions was complicated and the EAG found conflicting numbers for each group and phase in the CS and trial CSRs. The EAG suspected that this was due to the data being reported in separate sections that refer to different analysis sets. The EAG has included an overview of the participant flow through the different study phases in Figure 2, though due to the reason above, these numbers may differ from those reported in places in the CS. The EAG was unable to identify participant numbers for some stages of the participant flow. The company stated that data was missing from the analyses due to missing assessments during the COVID-19 pandemic and the exclusion of data from one of the trial sites (site 710). The number of participants discontinuing from the TRuE-V1 and TRuE-V2 trials was limited, with fewer than 10% of participants discontinuing in each arm. However, there were moderate levels of drop out during the TRuE-V-LTE, and across the trial phases this resulted in an approximate 20% loss of participants treated with ruxolitinib in the TruE-V-LTE endpoints. The EAG was unclear to what extent the missing data was due to drop-out from the trial or whether a number of participants did not meet the company's criteria for entry (i.e. no safety concerns with continuing ruxolitinib). In general, across the trial phases, the most common reasons for drop-out were those that could plausibly relate to efficacy or safety (e.g. withdrawal by participant, loss to follow-up). Given the magnitude of missing data and the potential for missing data to not be missing at random, the EAG considered that a 20% discontinuation rate could meaningfully affect treatment outcomes in the TRuE-V-LTE, and that appropriate missing data analysis would be influential. However, while imputation of missing data was conducted for the TRuE-V1 and TRuE-V2 trials (where missing data was minimal), this was not conducted for the TRuE-LTE (based on evidence in the CS). The EAG therefore considered that efficacy data from 52 weeks onwards in the submitted evidence base was at a high risk of attrition bias (see Section 3.2.2.6).

Figure 2: Participant flow in the pooled TRuE-V1 and TRuE-V2 trials, including the OLE and LTE



Note: aside from screening failures, where % represents the proportion of those screened who did not meet trial eligibility criteria, all other %s are calculated using the number of participants who received treatment during the double-blind period as the denominator.

Abbreviations: LTE, long-term extension; OLE, open-label extension

3.2.2.2. Population

The population in the NICE final scope was people aged 12 years and older with NSV with facial involvement. The TRuE-V1[18] and TRuE-V2[19] trials were based in 45 and 49 study centres respectively, and these centres were located in North America and Europe. No centres were located in the UK but the EAG understand the vitiligo care received in the site locations to be generalisable to the UK.

Trial eligibility criteria

Eligibility criteria for the TRuE-V1[18] and TRuE-V2[19] trials were provided in the CS (Document B, Table 6). The MHRA granted marketing authorisation for ruxolitinib[1] was broadly consistent with the eligibility criteria of the TRuE-V1 and TRuE-V2 trials. The therapeutic indication for ruxolitinib was treatment of NSV with facial involvement, however the license does not restrict to use on the face and it can be applied to any depigmented skin areas. The company have positioned ruxolitinib as a 2nd line treatment option, after TCS and TCIs, and if approved in this position, the population treated in NHS practice would likely be a subset of the population recruited to TRuE-V1 and TRuE-V2 trials. This was further discussed in Section 2.4 and Key Issue 2.

Prior to randomisation, 920 participants were screened for inclusion in the trial and 259 (28.2%) were deemed to be 'screening failures'. At the clarification stage (question A12), the EAG requested comment from the company on what appeared to be high numbers of screening failures and the reasons for this. The company stated that the specific criteria not met during screening were not collected. The EAG's clinical expert considered that the trial participants were nevertheless representative of the target population.

Participants who were enrolled and receiving treatment in either TRuE-V1[18] or TRuE-V2[19], were currently tolerating ruxolitinib cream, and presented no safety concerns for investigators, were invited to join the TRuE-V LTE[9] treatment extension trial. As such, this trial did not represent the whole target population of people eligible to receive ruxolitinib, but instead represented a subset of people who tolerated treatment. There were two components within TRuE-V LTE based on a

person's response to treatment in the TRuE-V1/TRuE-V2. People who had F-VASI90 at the end of TRuE-V1/TRuE-V2 entered a comparative trial and were randomised to either ruxolitinib or vehicle cream. People who did not have F-VASI90 joined a single arm trial using ruxolitinib. The EAG noted that in other places in this submission F-VASI75 is defined as a clinically meaningful response but that is not considered sufficient to enter the TRuE-V LTE RCT component.

Baseline characteristics

The demographic characteristics and baseline disease characteristics of the ITT populations from the TRuE-V1[18] and TRuE-V2[19] trials are reported in Table 7 and Table 8 of the CS (Doc B). Full baseline characteristics were not presented solely for the previously treated subgroup.

The treatment groups were well-balanced in demographic characteristics. Five hundred and fifty-two (81.9%) were White, 32 (4.7%) Black/African American, 28 (4.2%) Asian, 37 (5.5%) other, and 25 (3.7%) not reported. The race of participants was broadly representative of the UK 2021 Census data that reported that 82% of people in England and Wales were White and 18% belonged to a Black, Asian, mixed or other ethnic group[20]. Subgroup analysis presented in Figure 18 of the CS (Doc B), reported a similar response rate in the proportion of participants reaching F-VASI75 at week 24 across the race categories.

Participants' skin types were assessed using the Fitzpatrick skin phototypes (FSP) scale that classified skin from types I to VI. The original FST classifications included skin types I through IV; skin types V and VI were later added which correspond to people of Asian, Indian, and African origin. Most of the participants in the trial had Fitzpatrick Skin Type II, III and IV (88.9%). It was unclear if the skin types of the participants were representative of the population with vitiligo in England and Wales, but as noted, the race of the participants was broadly in line with the 2021 census data.

The baseline disease characteristics were also well-balanced between treatment groups. The mean time since diagnosis was 14.79 years with a median of 11.97 years since diagnosis. The EAG's clinical expert considered that this was consistent with more long-standing disease and noted that people with long-standing vitiligo may be less responsive to treatment. The company did not present subgroup data to compare treatment response according to time since diagnosis, and the EAG was therefore unclear to what extent this would be a treatment effect modifier.

As noted in Section 2.4, the company proposed positioning ruxolitinib as a new line of therapy in between the current 1st and 2nd line therapy in the BAD guidelines[21]. This would position it as a treatment for people whose condition had not responded to TCS and/or TCI, or for whom TCS or TCI are contraindicated. This would be prior to use of NB-UVB with or without TCS or TCI or oral betamethasone for those with rapidly progressing disease. Sixty-one per cent of participants in the TRuE-V1/TRuE-V2 trials had received prior therapy for vitiligo (Table 8, Doc B). Similar proportions in the trial had previously used TCS (28.0%), TCIs(31.8%), and NB-UVB (31.9%), to treat their vitiligo. Based on the evidence presented by the EAG, it was not possible to determine the proportion of participants in the trials for whom the disease had not responded to TCS and/or TCI, or for whom TCS or TCI were contraindicated, not tolerated or otherwise medically inadvisable. It was also not possible to determine the overlap between the number of participants who had previously received each previous treatment. However, a proportion of the trial participants had not received either TCS or TCSs at baseline, while nearly a third of participants had received NB-UVB, a later line of treatment. It was unclear how generalisable the full trial population was to the proposed 2nd line population for ruxolitinib.

The demographic characteristics and baseline disease characteristics of the participants in the TRuE-V LTE trial were reported in Table 9 and Table 10 of the CS (Doc B). The treatment groups in Cohort A were well balanced for baseline demographic and disease characteristics. All participants entering Cohort B were treated with ruxolitinib and were presented in groups based on their treatment arm in the TRuE-V1 and TRuE-V2 trials.

The participants entering the TRuE-V LTE (Cohort A and Cohort B) trial were a subset of those recruited to TRuE-V1/TRuE-V2, who tolerated treatment and wished to continue in the trial. The participants entering Cohort A and Cohort B had similar demographics and baseline characteristics to those recruited to TRuE-V1/TRuE-V2. However, the EAG noted that a higher proportion of participants in Cohort A had received prior therapy for vitiligo than the ITT population in TRuE-V1/TRuE-V2 (71.6% compared to 61.0%).

3.2.2.3. Intervention

Participants randomised to ruxolitinib applied the treatment twice daily for 24 weeks to all vitiligo areas on the face and body. Consistent with the product licence, the recommended dose was a thin layer of cream applied twice daily to the depigmented skin areas up to a maximum of 10% of BSA, with a minimum of 8 hours between two applications[1]. Ten per cent BSA represents an area as large as 10 times the palm of one hand with the 5 fingers. In the trials, participants were

given one 60-gram tube of ruxolitinib each week, equivalent to up to 240 grams over a four-week period. This is inconsistent with the product licence for ruxolitinib, which specified that no more than two tubes of 100 grams a month should be used.

A summary of exposure was presented in Table 37 of the EMA SmPC reported (provided in Appendix C of the CS), which has been adapted below in Table 8. The median weight of ruxolitinib applied in the trials was 4.07 grams per day but the mean (SD) dose was substantially higher at 7.36 (25.2) grams per day. Also, the EAG noted that the maximum dose applied was 237.1 grams per day. Therefore, at least one participant was applying substantially more ruxolitinib each day than the licence indicates. Based on the data provided by the company, the EAG was unable to determine how many trial participants used more than the licenced dose of ruxolitinib. The EAG was unclear how higher doses of ruxolitinib would affect clinical outcomes in the trial. The Phase II trial of ruxolitinib (see Section 3.2.2) included a dose comparison and showed that increased efficacy is possible with higher doses of ruxolitinib, but the highest dose used in the trial was the licensed dose and so efficacy evidence is not available for a higher dose. The safety implications of higher ruxolitinib doses were also unclear. The dose of ruxolitinib and the implications of assumptions around dosing is further discussed in relation to the economic model in section 4.2.4 and in Key Issue 4.

The licence for ruxolitinib specified that it should be used cutaneously only and that people should avoid washing treated skin for at least two hours after application.[1] Other topical medicinal products used to treat other conditions on the same skin areas should be applied with a minimum of two hours after the application of ruxolitinib. This was also applicable to the use of sunscreen or emollients, and in the trial these were required to be removed from the skin prior to applying ruxolitinib. In the trials, this restriction also applied to the use of camouflage make up. The EAG considered that these restrictions were sensible but may nevertheless be challenging to adhere to in practice. People with vitiligo are encouraged to maintain consistent use of sunscreen to protect depigmented skin, and people may also use camouflage make-up to reduce the impact of their condition. The EAG considered it plausible that in practice, adherence to these restrictions may be challenging around daily activities. This may reduce the effectiveness of ruxolitinib in practice. Clinical advice to the EAG was that the application of topical treatments is burdensome for people with vitiligo, and therefore the use of ruxolitinib with these restrictions may be equally or more burdensome.

Compliance of > 80% of the drug applications over the double-blind period for both the ruxolitinib and vehicle cream treatment arms in the TRuE-V studies was 98.1% (Table 3.1.2.1 in the TRuE-V1 CSR and TRuE-V2 CSR). However, participants (n = 13) from study site 710 in TRuE-V2 were excluded from the study due to non-compliance with the protocol and concerns with data quality. The EAG requested clarification (question A7) on how these participants were identified and the company noted that participants were not excluded from site 710, but that data from all participants at site 710 was excluded. The company did not offer any specific detail of the non-compliance with the protocol or why there were concerns with data quality. In the EMA SmPC report, the authors reported that the decision to exclude the data was due to "one critical finding (informed consent) and two major findings (source documents and organisation and personnel)" (p.103). Given the low numbers of people excluded from the trials, the EAG did not consider that the exclusion would meaningfully affect clinical outcomes, but still considered this to be an uncertainty in the appraisal.

Table 8. Summary of exposure in TRuE-V1/TRuE-V2 (adapted from Table 37, CS Appendix C [SmPC report])

Variable	Vehicle cream BID (N=224)	Ruxolitinib 1.5% cream BID (N=449)	Total (N=673)
Duration of treatment (days)			
Mean (SD)	156.8 (38.9)	158.9 (35.0)	158.2 (36.3)
Median	168.0	168.0	168.0
Min, max	1.0, 248.0	1.0, 237.0	1.0, 248.0
Average weight of medication applied (g)			
Mean (SD)	7.12 (22.96)	7.36 (25.23)	7.28 (24.48)
Median	3.81	4.07	4.03
Min, max	0.3, 236.3	0.4, 237.1	0.3, 237.1

Abbreviations: BID, twice daily; SD, standard deviation

In section 6.6 and 6.7 of the TRuE-V1 and TRuE-V2 protocols, the company described the treatments, vaccinations, and devices allowed or disallowed before, during, and/or after study treatment. Participants were permitted to use bland emollients, camouflage makeup, and a mineral-based sunscreen at least 2 hours after study drug application. However, participants should not use any other treatments for vitiligo at any time during the study. This included corticosteroids (topical, systemic, or oral), vitamin D derivatives, calcineurin inhibitors, laser or surgical treatments, NB-UVB, or other procedures. In addition, skin bleaching treatments, depigmenting agents, biological therapies, immunosuppressant agents, and live or live-attenuated vaccination were not permitted.

In section B.3.5.1 of the CS, the company stated that people receiving ruxolitinib and vehicle cream were assumed to use permitted concomitant therapies including vitamin D supplements, camouflage, fixing powder and sunscreen. The amount used for these therapies was not collected. In addition, a summary of concomitant medications used in the double-blind period was presented in the TRuE-V study CSRs (Table 1.4.3.1) as noted by the company at clarification (question A11). Concomitant medications were received by 73.5% of participants in the ruxolitinib arm, and 72.8% of participants in the vehicle cream arm. Table 1.4.3.1 of the trial CSRs provided details of the number of participants who received each concomitant medication, but the data presented were not sufficient to determine why they received the medication, the formulation of medication (oral/topical/inhaled), the dose, or how often it was used.

3.2.2.4. Comparator

Participants randomised to the control arm applied vehicle cream twice daily for 24 weeks to all vitiligo areas on the face and body. The number of tubes given to participants and the guidance for application was consistent with the ruxolitinib arm (Section 3.2.2.3).

A summary of exposure was presented in the EMA SmPC report Table 37 (CS Appendix C) and has been adapted as shown in Table 8. As with the ruxolitinib arm, the median weight of vehicle cream applied was substantially lower than the mean weight of vehicle cream applied. Also consistent with the ruxolitinib arm, the maximum dose applied far exceeded the intended dose (236.3 grams per day).

A discussion of background treatments received in the control arm can be found above in the

Intervention section (3.2.2.3).

3.2.2.5. Outcomes

The outcomes reported in the CS or accessible to the EAG during the timeframe of the appraisal are shown in Table 9. The outcome categories shown correspond to the outcomes specified in the NICE scope for this appraisal.

Response according to the VASI measures, facial or total, comprised the majority of the evidence base for ruxolitinib. The VASI measures consider both BSA and level of pigmentation of vitiligo patches, and so could be considered a composite outcome of these characteristics, both of which are important to people with vitiligo[22]. The company reported response according to various thresholds of change in F-VASI and T-VASI. Research indicates that the level of

response considered by people with vitiligo to be meaningful varies across the population. However, clinical advice and published research suggests that a 75% threshold is considered to be meaningful by most people with vitiligo (i.e. F-VASI75 and T-VASI75). Notably, the company did not account for multiple comparisons in the trial (see Section 3.2.2.6).

As noted previously, clinical advice to the EAG was that VASI assessments of vitiligo are a highly accurate measure vitiligo but are typically not used in practice due to the time needed to perform the assessment. This means that while these outcomes in the trial would be an accurate measure of change in vitiligo lesions, there may be some generalisability issues when interpreting the data (for example, clinical decisions on the basis of response may use alternative criteria in clinical practice).

HRQoL was assessed using three disease-specific instruments, though only data for the VitiQoL was assessed in detail by the EAG during the appraisal. In the CS, the company stated that no difference in HRQoL was found between arms on the DLQI and CDLQI, which are dermatology HRQoL measures, though the data was not presented. The VitiQoL measure was developed to measure the impact of vitiligo on quality of life, including how vitiligo has impacted people's ability to function, their relationships, physical health and emotional wellbeing. The measure has a moderate to poor association with self-reported vitiligo severity[23] and the EAG was unable to find a validated minimally clinical important difference (MCID) threshold, or evidence that the measure was responsive to change. The EAG was unclear why the company had selected not to incorporate a generic measure of HRQoL in its trials, such as the EQ-5D, particularly given the lack of psychometric validation of the VitiQoL. The items in the VitiQoL did not appear to assess additional potential impacts of vitiligo beyond those included in generic HRQoL instruments and this would have reduced uncertainty in the HRQoL effects of treatment.

Table 9: Clinical outcomes for ruxolitinib appraised by the EAG

	Pooled TRuE-V1 and TRuE-V2 **Double-blind phase (24-weeks)**	**Pooled TRuE-V1 and TRuE-V2** **Open-label phase (24 – 52-weeks)**	**TRuE-V-LTE Cohort A (Responders; ≥F-VASI90)** **Double-blind (52 – 103 weeks)**	**TRuE-V-LTE Cohort B (Non-responders; <F-VASI90)** **Open-label (52 – 103 weeks)**
Re-pigmentation	Facial and bodily vitiligo as assessed using F-VASI, F-BSA and T-VASI.	Facial and bodily vitiligo as assessed using F-VASI, F-BSA and T-VASI.	Facial vitiligo as assessed using F-VASI	Facial vitiligo as assessed using F-VASI

	Pooled TRuE-V1 and TRuE-V2 **Double-blind phase (24-weeks)**	**Pooled TRuE-V1 and TRuE-V2** **Open-label phase (24 – 52-weeks)**	**TRuE-V-LTE Cohort A (Responders; ≥F-VASI90)** **Double-blind (52 – 103 weeks)**	**TRuE-V-LTE Cohort B (Non-responders; <F-VASI90)** **Open-label (52 – 103 weeks)**
	Clinician- and patient-rated change in facial and total vitiligo.	Clinician- and patient-rated change in facial and total vitiligo.		
Maintenance of response	Change in F-VASI response	Change in F-VASI response	Relapse in F-VASI	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.	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	T-VASI Clinician- and patient-rated change in total vitiligo	-	-
Cosmetic acceptability	VNS	VNS	-	-
Adverse effects of treatment	Treatment-emergent AEs	Treatment-emergent AEs	Treatment-emergent AEs	Treatment-emergent AEs
Health-related quality of life	VitiQoL (separate for each trial) HADS	VitiQoL (separate for each trial) HADS	-	-

Abbreviations: AE, adverse events; F-BSA, facial body surface area; F-VASI, Facial Vitiligo Area Scoring Index; HADS, Hospital Anxiety and Depression Scale; T-VASI, Total Vitiligo Area Scoring Index; VitiQoL, Vitiligo-specific quality-of-life instrument; VNS, Vitiligo Noticeability Scale.

The company explored various analyses to accounting for missing data in the TRuE-V1 and TRuE-V2 trials. There was minimal missing data in these trials and the different approaches to analysis did not have a material impact on the results. However, as noted in Section 3.2.2.1, there was high rate of missing data in the TRuE-V-LTE phase of the trial, with a third of people involved in the earlier trial phases not enrolled. The company did not appear to employ the same level of investigation of the effect of missing data in this trial, and the EAG was concerned that missing data could not be determined to be missing at random. As a consequence, the

EAG had some concerns about the validity of the results from the TRuE-V-LTE trial (see Section 3.2.2.6).

3.2.2.6. Critical appraisal of the design of the studies

The company assessment of the quality of the TRuE-V1 and TRuE-V2 trials was reported in Appendix D of the CS, Table 9. The assessment utilised version 2 of the Cochrane risk-of-bias tool for randomised trials (RoB 2)[10]. The company concluded that both trials were at a low risk of bias in each domain assessed, but the company did not offer specific reasoning for the judgements.

A further quality appraisal for the TRuE-V1 and TRuE-V2 trials and the TRuE-V-LTE trial was presented in Table 5 (Section B.2.5) of Document B. The assessment for the TRuE-V1 and -V2 trials is presented in the same column, due to the comparability of the trial methods. This assessment was conducted using the "minimum criteria for assessment of risk of bias in RCTs" set out in CRD's guidance for undertaking reviews in health care[24]. The company provided specific reasoning linked to the rating for each domain of the assessment, though no overall risk of bias judgement was made. The company assessment did not appear to take account of any variation in risk across outcomes. The EAG considered the assessment conducted by the company was appropriate only for the RCT component of the TRuE-V-LTE trial and not the single arm component.

Quality assessment of the trials of ruxolitinib

In general, the EAG agreed with the company's appraisal of the TRuE-V1 and TRuE-V2 trials as assessed using the CRD checklist. In addition to the ratings provided by the company, however, the EAG noted that:

- a minority of people (20%) in the vehicle cream arm showed a meaningful response to treatment as assessed on the F-VASI50 during the double-blind phase of the TRuE-V1 and -V2 trials, even though other active treatments for vitiligo were prohibited. The EAG therefore considered that relative effect estimates from the trial (i.e., the difference between treatment arms) would be more reliable than absolute effects (i.e. the magnitude of the response in the ruxolitinib arm), and that this assumption should apply to all outcomes. Accordingly, the EAG considered that the results from the treatment extension period were at a higher risk of bias.

- The company did not adjust for multiplicity in the analysis, which means that there is an increased risk of a type I error (i.e., incorrectly concluding that there is a statistically significant treatment effect)

- The EAG noted that the upper range in received doses of ruxolitinib and vehicle cream exceeded the recommended dose by a considerable margin. The EAG requested but did not receive detailed information from the company about the dose received by participants in the trial (clarification question B10) and therefore were uncertain how many people who received ruxolitinib in the trials exceeded the dose that is recommended by the product licence. The EAG was uncertain to what extent this would have affected treatment effect estimates in the trials, however considered that this was a potential source of uncertainty.

- The company appraisal did not note that the treatment extension (24 – 52 weeks) was open-label. Open-label trials increase the risk of detection bias, as knowledge of the intervention received can affect the measurement of outcomes.

The company assessment of the TRuE-V1 and TRuE-V2 trials rated the risk of selection bias to be low, on the basis that all outcomes were reported in the trial CSRs. However, the EAG considered the risk of selection bias to be high in the CS, as not all scoped outcomes were presented fully in the main submission (Document B).

For the double-blind phase of the TRuE-V-LTE trial (Cohort A), the EAG did not fully agree with the company's appraisal, for the following reasons:

- The assessment did not take into account in the risks of re-randomising a sub-population of participants selected from the previous trials on the basis of treatment outcome. Participants entering the TRuE-V-LTE were those with no safety concerns after receiving ruxolitinib, as judged by the investigator, and those who had completed the study (which may be influenced by treatment efficacy). This naturally leads to a risk of selection bias in the trial.

- The company's assessment of dropouts from the trial considered differential drop out between arms only and did not consider the high absolute rate of attrition in the trial (approximately 30% in the ruxolitinib arm and 15.5% in the vehicle cream arm). The most common reasons for drop out from the trial were reasons related to treatment outcome. The EAG considered the high rate of missing participants to also represent a risk of bias, in addition to the differential rate between arms.

- The company referred to a 'Table 8' for the methods used to account for missing data. The EAG assumed that this was a typo and the company meant to cite Table 12, which describes the methods for statistical analysis used in the TRuE-V-LTE trial. The methods described in this table would not be sufficient to account for the missing data in the trial, and are more simplistic than those used in the TRuE-V1 and TRuE-V2 trials (which had minimal missing data). The EAG considered that the outcomes from the TRuE-V-LTE trial were at a high risk of bias because of missing data.

As with the earlier trials, the company rated the TRuE-V-LTE trial as being at a low risk of selection bias as all outcomes were reported in the trial CSRs. However, the EAG considered the trial reporting in Document B of the CS to be at a high risk of selection bias, as results were not fully reported.

For the single-arm cohort of the TRuE-V-LTE trial (Cohort B), as noted in Section 3.1, the company used an inappropriate tool (the CRD checklist for RCTs). Within the timeframe of the EAG appraisal, it was not possible for the EAG to conduct a formal quality appraisal using an appropriate tool. However, informally, the EAG noted the following issues:

- Single-arm trials are subject to a high risk of bias as they cannot control for the possibility that factors other than the treatment may influence treatment outcomes; for example, natural changes in the condition over time.
- There is a risk of selection bias, as participants were selected from the previous trials on the basis of treatment outcome.
- As noted by the company, the trial was open-label, which introduces additional bias, such as detection bias.
- There was a high rate of missing data (>20% participant attrition), which was not accounted for in analyses. The most common reasons for discontinuation from the trials were related to treatment outcome.

Quality assessment of outcomes in the prior therapy subgroup using the TRuE-V1/TRuE-V2

The EAG were aware that the effectiveness data used in the economic model primarily came from the "prior therapy" subgroup. Given that this was the clinical data primarily used in the economic model, the EAG undertook quality assessment for this subgroup using the tool taken from CRD's guidance for undertaking reviews in health care (Table 10, below). The appraisal was based on information available to the EAG, which did not include full participant characteristics and outcome data for the previously treated subgroup (Key Issue 2). The EAG concluded that the outcomes linked to the TRuE-V1/TRuE-V2 prior therapy subgroup are at high risk of bias. This was primarily because it was unclear if the treatment arms were similar at the outset, there were no details of how many participants in the subgroup withdrew from the trial or whether this was similar between treatment arms, poor reporting of the outcomes, and a lack of clarity about the analysis used.

Table 10. Quality assessment of the outcomes linked to the TRuE-V1/TRuE-V2 prior therapy subgroup

	TRuE-V1 and TRuE-V2 prior therapy subgroup
Was the method used to generate random allocations adequate?	Participants were centrally assigned to study treatment using an interactive response technology system. Participants were not stratified by prior therapy and this analysis breaks randomisation.
Was the allocation adequately concealed?	Yes, allocation generated by automated system
Were the groups similar at the outset of the study in terms of prognostic factors?	It was unclear if the groups were similar at outset. The company provide the total number of participants in the prior therapy subgroup in Table 32 (Doc B) but no baseline characteristics by treatment arm.
Were the care providers, participants, and outcome assessors blind to treatment allocation?	Yes, double-blind design
Were there any unexpected imbalances in dropouts between groups?	It was unclear how many participants in the subgroup withdrew from the trial or whether this was similar between treatment arms.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	As noted in Key Issue 2, at clarification (QA2) the company were invited to provide evidence for the prior treated subgroup, however this was submitted in a series of inadequately labelled appendix tables including superfluous data, rather than as a transparent submission of selected and pooled estimates from the trials.
Did the analysis include an ITT analysis? If so, was this appropriate	This was the analysis of a subgroup rather than an ITT analysis. It was unclear what methods were used to account

	TRuE-V1 and TRuE-V2 prior therapy subgroup
and were appropriate methods used to account for missing data?	for missing data in the previously treated subgroup, as the data were not provided. However, multiple imputation was used for the ITT analysis.

Abbreviations: ITT, intention to treat

3.2.3. Description and critique of the results of the studies

3.2.3.1. Clinical effectiveness results

Clinical effectiveness data in the CS was largely based on pooled data from the TRuE-V1[25] and TRuE-V2[19] trials. Overall, the EAG considered that the company's evidence submission was poor and lacking in transparency. Not all scoped outcomes were presented by the company. In some cases, the company referred the EAG to documents produced by the EMA in the SmPC report of ruxolitinib(EMA)[26] (provided in Appendix C of the CS), though some of these data were only available in poor resolution figures and lacked detail (note that SmPC reports are not produced with the aim of being submitted for appraisal within the HTA process). Some data required by the NICE decision problem were only available in trial CSR documents and appendices. Notably, this included clinical effectiveness outcome data for the previously treated subgroup, which were not in the CSR documents provided by the company (though the EAG requested that all CSR files, including tables and appendices be submitted [clarification question C2]) but were submitted by the company in a series of files at clarification that appeared as if they were originally an appendix to the CSRs. These were poorly labelled, which led to uncertainty about the data source. In some cases, the EAG attempted to calculate data for the pooled trial population from the individual CSRs, to aid comparability with other trial outcomes, but noted that these data would not consider missing values analysis and may be based on different analysis populations than data reported in the CS.

Overall, the poor reporting standard of clinical effectiveness evidence in the CS and in subsequent submissions from the company undermined the ability of the EAG to fully appraise the clinical effectiveness of ruxolitinib. The EAG also considered there to be a risk of selection bias in the CS (Section 3.2.2.6). In particular, the EAG was concerned about the reliability of data for the previously treated subgroup, which is the company's chosen indication for ruxolitinib and is the population used in its economic evaluation (Key Issue 2).

In this section, the EAG provides a summary of its appraisal of the clinical effectiveness evidence for all scoped outcomes in the main trial population (i.e., regardless of previous

treatment status). Due to the reasons outlined above, the appraisal may have gaps or be uncertain in places.

Change in facial vitiligo

The response rate for the ITT population from the pooled trials on the F-VASI at 50%, 75% and 90% is shown in Table 11 alongside the mean change in the F-BSA scale. The EAG noted that a significant minority (20%) of people in the vehicle cream arm showed a >50% reduction in facial vitiligo (F-VASI) in the 24 weeks from baseline, even though active treatments for vitiligo were prohibited during the trial. The EAG was uncertain what would cause this effect, as it was unclear to what extent the F-VASI measure would be susceptible to subjectivity bias. Given the high rate of response in the vehicle cream arm, the EAG considered that the relative treatment effects for all outcomes during the double-blind trial phases would be most reliable for determining the effectiveness of ruxolitinib (i.e., as opposed to the absolute data in each arm). The EAG also considered that outcomes from the uncontrolled trial phases (the treatment extension and Cohort B analysis of the LTE) may best be interpreted with caution.

The data demonstrated that ruxolitinib was more effective than vehicle cream at reducing facial vitiligo, as assessed across all outcomes and accounting for imprecision in the treatment effects. In the 24 weeks from baseline, 21% more people receiving ruxolitinib achieved a response that was above the threshold considered by the EAG's clinical expert to be clinically meaningful to people with vitiligo (i.e. F-VASI 75%) compared to vehicle cream. The effect of ruxolitinib on the F-VASI increased further between week 24 and 52, with more people initially allocated to ruxolitinib achieving a greater level of response by the 52-week timepoint. By 52 weeks, half of all those initially allocated to ruxolitinib had achieved a response above the threshold considered to be clinically meaningful (i.e. F-VASI 75%). This was 40% more people than had achieved a response with vehicle cream at 24 weeks.

Figures provided by the company (Figure 10 and 11, CS Doc B p.66 & 70) showed an increasing response rate to treatment over time; for example, the number of people achieving F-VASI75 following ruxolitinib increased from 5.3% at 8 weeks (no difference with vehicle cream) to 31.0% at 24 weeks. In the treatment extension, response rates in those switching to ruxolitinib appeared to follow the same trajectory as those allocated to ruxolitinib in the initial double-blind phase.

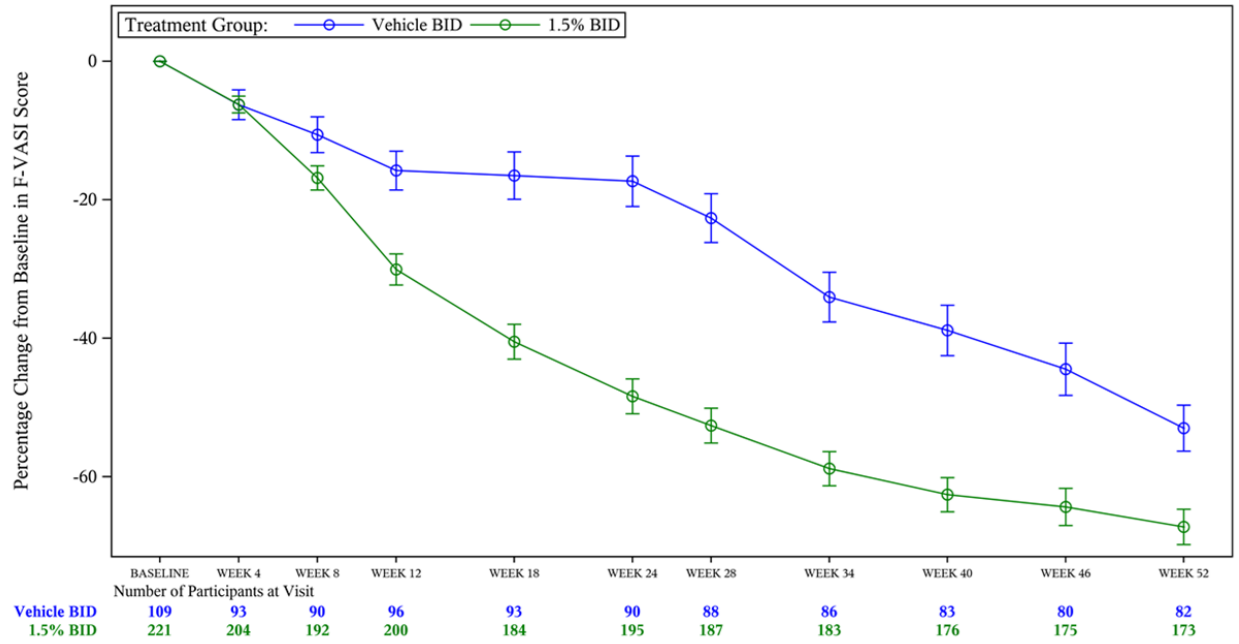
Mean change in F-VASI score in the two trials was shown in figures only in the SmPC and in the respective trial CSRs (showing change in F-VASI scores with respective standard errors). The EAG was unable to identify specific data, including mean, median, min and max change in any of the documents supplied by the company (the trial CSRs received by the EAG reported the data in figure form only). The figures are reproduced below (Figure 3). The figures showed a steady increase in the treatment effect of ruxolitinib over time, though standard error bars suggested that this effect varied meaningfully across the population. This was consistent with the response rate data, showing that many participants in the trials did not experience a clinically meaningful response to ruxolitinib. The EAG also noted that the curve gradient began to plateau from week 34 onwards, suggesting that limited further improvements in facial vitiligo may occur beyond this timepoint. This effect was also visible in mean T-VASI scores (see next section and shown on p.166 of the SmPC report)[1].

Table 11: Change in facial vitiligo outcomes based on pooled data from TRuE-V1 and TRuE-V2

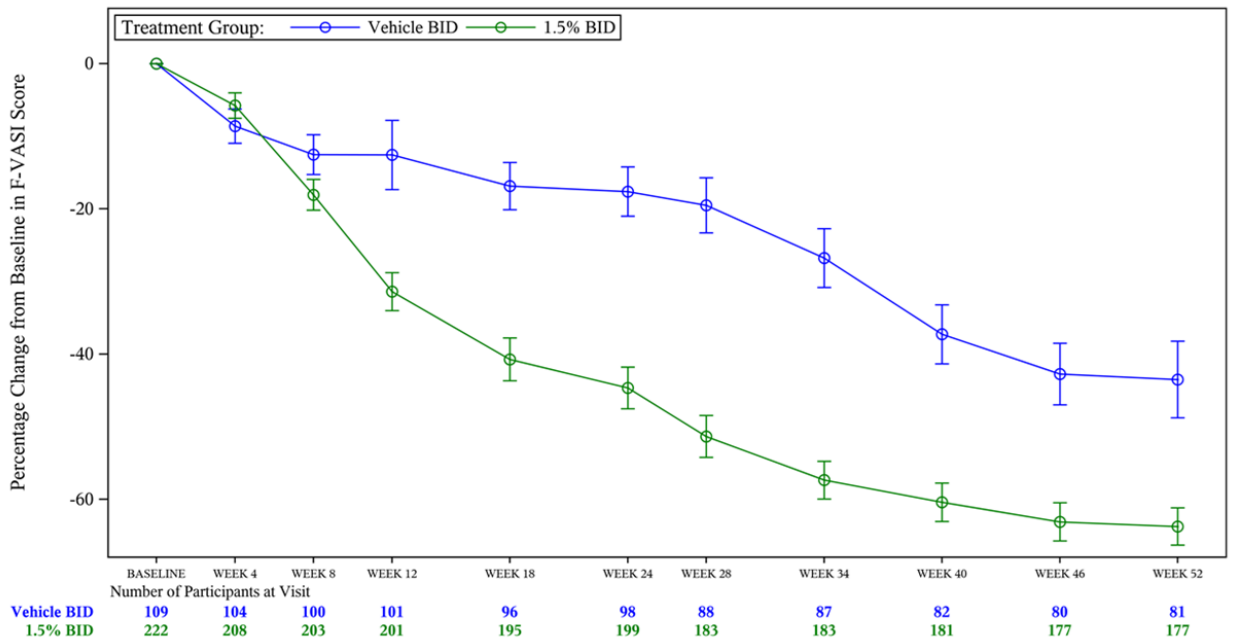
	Response rate						% LSM change	
	F-VASI50		F-VASI75		F-VASI90		F-BSA	
	Vehicle (N=218)	Rux (N=443)	Vehicle (N=218)	Rux (N=443)	Vehicle (N=218)	Rux (N=443)	Vehicle (N=218)	Rux (N=443)
Week 24	19.6% (SE 2.89)	51.7% (SE2.46)	9.6% (SE2.17)	30.7% (SE2.29)	1.9% (SE1.01)	16.0% (SE1.83)	-7.9% (95%CI -13.02, -2.69)	-27.8 % (95%CI -31.29, -24.41_)
Difference between arms		32.2% (95%CI 24.6, 39.7)		21.1% (95%CI 14.9, 27.3)		14.2% (95%CI 10.1, 18.3)		-20.0% (95%CI -26.2, -13.8)
OR (95%CI)		4.40 (2.92, 6.65)		4.17 (2.43, 7.14)		10.33 (3.31, 32.2)		NA
	Vehicle – Rux (N=163)	Rux – Rux (N=350)	Vehicle – Rux (N=163)	Rux – Rux (N=350)	Vehicle – Rux (N=163)	Rux – Rux (N=350)	Vehicle – Rux (N=163)	Rux – Rux (N=350)
Week 52	52.8%	74.6%	28.2%	50.3%	14.1%	30.3%	-26% (-22, -30)	-42.5% (-41, -44)

Note: Response rate data is estimated based on the company's analyses (described in section B.2.4 of the CS). All data shown are using the company's multiple imputation approach. Data at 52 weeks was taken from figures provided in the EMA SmPC report. Data for F-BSA was approximate based on figure curves and error bars and therefore may be inaccurate. Data from study site 710 were removed from all data points.

Figure 3: Change (mean ±SE) in F-VASI in TRuE-V1 and TRuE-V2



Note: Data from study site 710 were excluded.



Note: Data from study site 710 were excluded.

Note: source EMA SmPC, appendix C of the CS (p.115)

Physician- and patient-reported assessments of improvement in vitiligo were not reported in the CS. The company cited the SmPC report[1], which presented the results separately for the two trials. The EAG calculated a naïve pooling of the trials, shown in Table 12. The results were consistent with results from the F-VASI scales.

Table 12: Physician- and Patient-reported improvement in facial vitiligo from TRuE-V1 and TRuE-V2

	Vehicle cream (N=109)	Ruxolitinib (N=221)
F-PhGVA score of clear (0) or almost clear (1)		
Week 24	9.04%	30.75%
Week 40	21.74%	40.28%
Week 52	27.61%	42.82%
F-PaGIC V score of very much improved (1) or much improved (2)		
Week 24	7.98%	42.64%
Week 40	32.73%	50.28%
Week 52	38.04%	53.14%

Source: calculated based on data reported in the SmPC[1]

Note: data from study site 710 were excluded

Maintenance of response in facial vitiligo

The EMA SmPC[1] report provided shift summary data for those receiving ruxolitinib across both trials for week 24 to 52, which showed how participants' treatment response changed between these time points. These data are reproduced below (some participants were missing from these data [n=44], implying that multiple imputation was not used). The reasons for missingness were not reported and so it's possible that some data were missing due to treatment outcome (see critical appraisal of the included trials, section 3.2.2.6). The data showed the following:

- A minority of people (10.3%) experienced a deterioration in treatment response between 24- and 52-weeks.
- Approximately a third of people (38.8%) remained in the same response category between week 24 and week 52

- In all categories under F-VASI-90 (the highest response), more people (51.5%) showed a further improvement in response between week-24 and -52 than remained in the same category.

Table 13: Shift summary of maintenance response on F-VASI (ITT pooled population) from week 24 to week 52 (ruxolitinib arm)

Response at Week 24		Response at Week 52					
Value	n (%)	< F-VASI25	F-VASI25 to < F-VASI50	F-VASI50 to < F-VASI75	F-VASI75 to < F-VASI90	F-VASI90	Missing
Pooled analysis							
< F-VASI25	131 (33.2)	47 (35.9)	21 (16.0)	30 (22.9)	7 (5.3)	8 (6.1)	18 (13.7)
F-VASI25 to < F-VASI50	59 (15.0)	0	9 (15.3)	21 (35.6)	12 (20.3)	4 (6.8)	13 (22.0)
F-VASI50 to < F-VASI75	82 (20.8)	1 (1.2)	8 (9.8)	26 (31.7)	22 (26.8)	19 (23.2)	6 (7.3)
F-VASI75 to < F-VASI90	58 (14.7)	0	2 (3.4)	7 (12.1)	22 (37.9)	26 (44.8)	1 (1.7)
F-VASI90	64 (16.2)	1 (1.6)	0	1 (1.6)	7 (10.9)	49 (76.6)	6 (9.4)

Note 1: Data from participants enrolled at Site 710 in Study INCB 18424-307 were excluded.
Note 2: The analysis was conducted in the ITT population for participants in the ruxolitinib 1.5% cream BID group with nonmissing F-VASI scores at Week 24.

Source: EMA SmPC report, p. 124

The company reported shift summary data for the TruE-LTE trial between week 52 to week 104 for those receiving ruxolitinib who did not respond to treatment (i.e., those who received ruxolitinib in the original trials who did not respond, entered cohort B and continued to receive ruxolitinib; CS Doc B p.121). These data showed that continuing improvement in F-VASI was possible beyond week 52, but that a deterioration in response was also possible. Again, some data were missing from these data ([redacted]%), and as reasons for missingness could include reasons related to treatment efficacy, the precise rates of movement between response category were uncertain.

Facial vitiligo outcomes for responders (Cohort A) at week 104 in the TruE-V LTE trial are shown in Table 14**Error! Reference source not found.**. The EAG had concerns about these data on the basis that a reasonable minority of participants in both arms were censored due to treatment discontinuation: 23.2% in the vehicle cream arm and 12.7% in the ruxolitinib arm. The EAG was unable to identify the reasons for discontinuation of these participants from the

information provided by the company, however in general the biggest reason for discontinuing from the trials was loss to follow up and withdrawal by participant. The EAG considered it plausible that these discontinuations would not be random, but participants would have discontinued due to the efficacy or safety of treatment. The EAG considered that the number of participants missing from this analysis at 104 weeks was sufficient to potentially bias the results, and therefore considered that the data should be interpreted with caution. To account for this, the EAG calculated relapse rates in each arm to include those who discontinued the trial (i.e. assuming all who discontinued the trial relapsed) and/or those who received rescue medication (i.e. those who received ruxolitinib to maintain a response; note that the EAG was unclear how this was administered in those who were continuing with ruxolitinib during the LTE). These data are also shown in Table 14.

Based on the number of people shown to have experienced a relapse and according to the company's calculation (<FVASI75), 14.5% of people who responded to ruxolitinib relapse within 2 years while still receiving treatment. However, when including all those who discontinued treatment, 27.3% of people who continue treatment with ruxolitinib will relapse within 2-years, and this was 30.9% when also including those who received rescue medication. Continuing with ruxolitinib after achieving a response was nevertheless associated with a reduced risk of relapse: twice as many people who discontinued ruxolitinib experienced a relapse than those who continued with treatment. The rate of relapse after discontinuing treatment was 28.6%, or 60.7% if including all those who discontinued the trial and received rescue treatment.

At the time of submission, the median time to relapse was not estimable in either group and the relative hazard for relapse was highly imprecise. However, the EAG was persuaded that continuing with ruxolitinib was likely to reduce the risk of relapse compared to discontinuation.

Table 14: F-VASI75 at week 104 for those who responded in the TRuE-V1 and TRuE-V2 trials

	Responders	
	Switched to vehicle (N=56)	Continued with rux (N=55)
<F-VASI75 (relapse); N (%)	16 (28.6%)	8 (14.5%)
Time to F-VASI75 (relapse); days (95%CI)	NE (238.0, NE)	NE (NE, NE)
HR (95%CI)		0.422 (0.18, 0.99)
<F-VASI75 (relapse) including those censored for tx discont	29 (51.8%)	15 (27.3%)

	Responders	
<F-VASI75 (relapse) including those censored for tx discont and those who received rescue therapy	34 (60.7%)	17 (30.9%)

Abbreviations: discont, discontinuation; F-VASI, Facial Vitiligo Area Scoring Index; HR, hazard ratio; NE, not estimable; rux, ruxolitinib

Change in total vitiligo

Only the rate of people meeting T-VASI50 was reported in the CS. To determine the response rates at other thresholds, the EAG identified data reported separately from the trial CSRs. The EAG has attempted to calculate response rates where feasible, but these do not account for censoring, and no continuous or variance data were available. The data available are shown in Table 15.

As with facial vitiligo outcomes, a minority of people in the vehicle cream arm reported meaningful improvements in bodily vitiligo, though this was lower than for F-VASI – approximately 6% of people who received vehicle cream were reported to have experienced a >50% reduction in total vitiligo during the 24-week DB period.

Response rates were lower for total vitiligo than facial vitiligo: 6.1% and 36.4% of people receiving ruxolitinib achieved a meaningful response in total vitiligo (T-VASI75) at 24- and 52-weeks, respectively, compared to 30.7% and 50.3% in F-VASI. The EAG considered it plausible either that (a) there may be different mechanisms involved in bodily and facial vitiligo, and therefore outcomes may not be well correlated, and/or (b) that bodily vitiligo was slower to change and that further improvements in bodily vitiligo may be seen with longer follow-up. The EAG was aware of evidence that some parts of the body (e.g., hands, feet, lips) may be less likely to respond to treatment for vitiligo than the face and trunk, but was unsure how established this effect is, whether it would be consistent across treatment types, and whether the effect would be sufficient to explain the difference between F-VASI and T-VASI outcomes. As shown in the next section, a similar proportion of people showed an improvement in response between 24-weeks to 52-weeks on the T-VASI as F-VASI, and on the whole the EAG did not consider there to be evidence of a delayed treatment effect for bodily vitiligo.

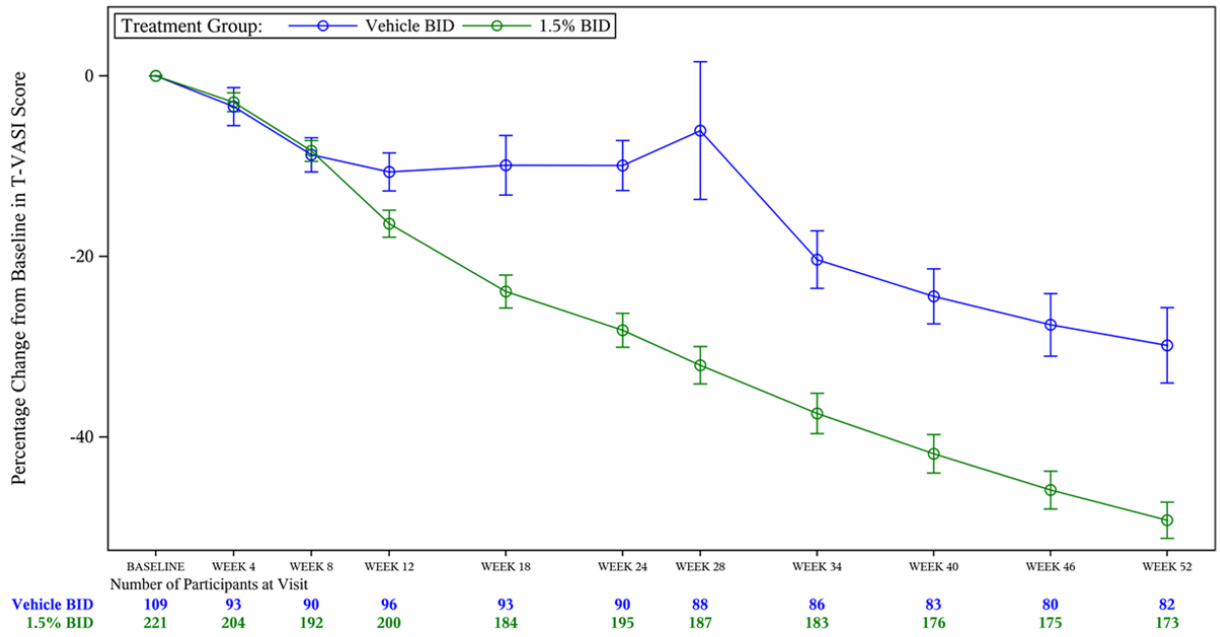
Table 15: Change in bodily vitiligo outcomes based on pooled data from TRuE-V1 and TRuE-V2

	Response rate					
	T-VASI50		T-VASI75		T-VASI90	
	Vehicle (N=218)	Rux (N=443)	Vehicle (N=218)	Rux (N=443)	Vehicle (N=218)	Rux (N=443)
Week 24	5.8% (SE 1.64)	21.9% (SE 2.04)	1.8%	6.1%	0%	0.68%
Difference between arms		16.1 (95%CI (10.9, 21.2)		NR		NR
OR (95%CI)		4.55 (2.42, 8.58)		NR		NR
	Vehicle – Rux (N=163)	Rux – Rux (N=350)	Vehicle – Rux (N=218)	Rux – Rux (N=443)	Vehicle – Rux (N=218)	Rux – Rux (N=443)
Week 52	27.0%	51.1%	7.3%	36.4%	1.8%	4.5%

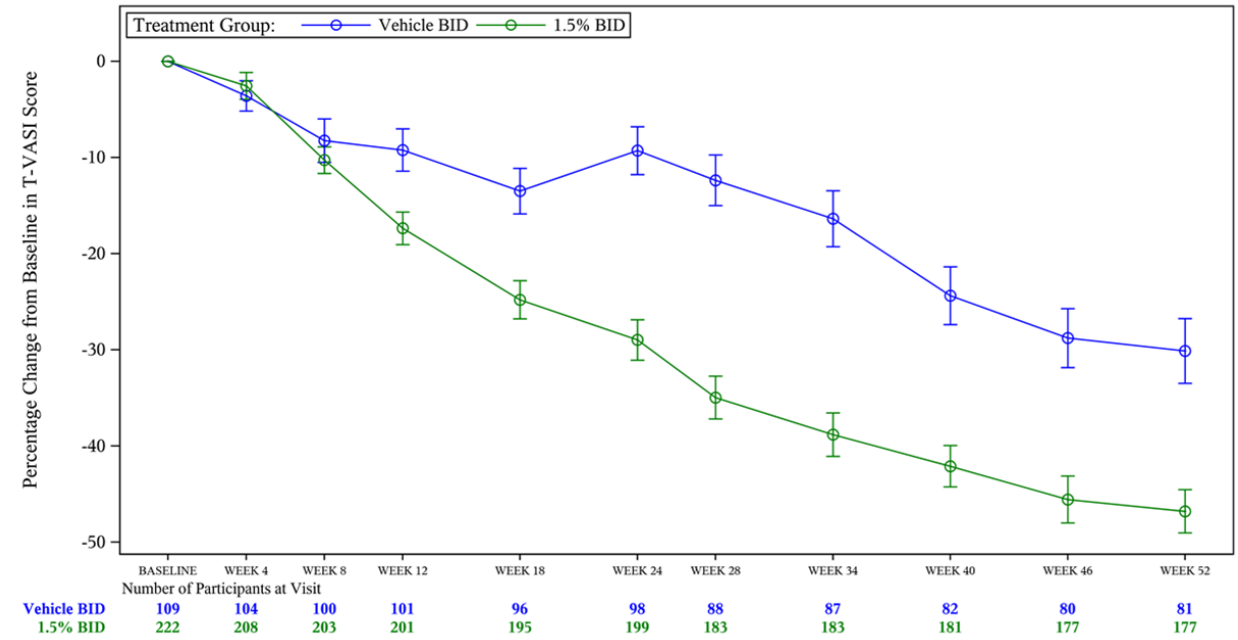
Note: week 52 data for T-VASI75 and T-VASI90 was taken from the CSR and was only available as a % from the ITT population using the company's multiple imputation analysis.

Mean change in T-VASI scores over the two trials was reported in the SmPC report and is shown in Figure 4.

Figure 4: Change (mean ±SE) in T-VASI in TRuE-V1 and TRuE-V2



Note: Data from study site 710 were excluded.



Note: Data from study site 710 were excluded.

Maintenance of response in total vitiligo

The shift summary data between week 24 and week 52 for T-VASI were reported in the EMA SmPC report. Of those who showed a response of ≥T-VASI-25 at 24 weeks, only 6.7% showed signs of relapse (reduction in response category) by 52-weeks. A third of participants (35.6%) remained in the same response category, and 50.3% of participants with a response <T-VASI90 at 24 weeks showed an improvement in response by 52-weeks.

Table 16: Shift summary of maintenance response on T-VASI (ITT pooled population) from week 24 to week 52 (ruxolitinib arm)

Response at Week 24		Response at Week 52					
Value	n (%)	< T-VASI25	T-VASI25 to < T-VASI50	T-VASI50 to < T-VASI75	T-VASI75 to < T-VASI90	T-VASI90	Missing
< T-VASI25	198 (50.3)	75 (37.9)	58 (29.3)	33 (16.7)	6 (3.0)	1 (0.5)	25 (12.6)
T-VASI25 to < T-VASI50	104 (26.4)	4 (3.8)	29 (27.9)	46 (44.2)	11 (10.6)	1 (1.0)	13 (12.5)
T-VASI50 to < T-VASI75	66 (16.8)	0	3 (4.5)	24 (36.4)	28 (42.4)	5 (7.6)	6 (9.1)
T-VASI75 to < T-VASI90	23 (5.8)	1 (4.3)	1 (4.3)	4 (17.4)	9 (39.1)	8 (34.8)	0
T-VASI90	3 (0.8)	0	0	0	0	3 (100.0)	0

Note: Data from participants enrolled at Site 710 in Study INCB 18424-307 were excluded.

Cosmetic acceptability

Response to treatment as measured by the VNS (a score of 4 or 5 indicating their vitiligo is no longer noticeable or a lot less noticeable) was reported in the CS. The data showed that a third of people who received ruxolitinib in the TRuE-V1 and TRuE-V2 trials considered their vitiligo to have become a lot less noticeable after 52 weeks' of treatment.

	VNS score 4 or 5	
	Vehicle (N=218)	Rux (N=443)
Week 24	4.2% (SE1.45)	22.5% (SE2.09)
Difference between arms		18.3% (95%CI 13.3, 23.2)

	VNS score 4 or 5	
OR (95%CI)		6.52 (3.11, 13.67)
	Vehicle – Rux (N=163)	Rux – Rux (N=350)
Week 52	16.6%	36.3%

Abbreviations: OR, odds ratio; rux, ruxolitinib; SE, standard error; VNS, vitiligo noticeability scale

Health-related quality of life

The CS, Document B, did not present HRQoL data evaluated in the trials. The company referred to the EMA SmPC report[1] (CS, appendix C), although this report did not contain data for the DLQI and the CDLQI, just stated that no changes in either outcome were observed over time (EMA SmPC, p.118). The trial CSRs[9,12,18,19] reported DLQI and CDLQI data at baseline and follow-up. Amongst adults, the majority of people reported that their vitiligo had no effect or a small effect on their lives at baseline as assessed using the DLQI. There was no change in DLQI or CDLQI over the trials.

Change in VitiQoL scores (a vitiligo-specific HRQoL measure) was reported separately for each trial in the SmPC report, and no statistically significant difference in scores was reported between groups at the end of the double-blind phase (week 24). The absolute change in HRQoL increased between week 24 and week 52[9,12,18,19], but no statistical tests were conducted to determine if the change from baseline was statistically significant. The company did not report a validated clinically minimally important difference for this measure, and the EAG was unable to identify one during its appraisal. As a consequence, the EAG was unable to determine if participants in either arm showed a clinically meaningful change in VitiQoL during the trials). However, using an arbitrary threshold of 10%, improvements in VitiQoL were <10% at week 24 and marginally above 10% at 52 weeks for those initially assigned to ruxolitinib in TRuE-V1[7] and <10% at all timepoints in TRUE-V2[8](though the EAG highlight that these rates do not account for change in the vehicle cream arm). Variance around VitiQoL scores was extremely wide, however: mean change from baseline at 52 weeks in those originally assigned to ruxolitinib was [redacted] in TRUE-V1, suggesting that effects of ruxolitinib on VitiQoL were extremely varied across the population. The company did not report change in HRQoL scores for those who reported that their condition had a meaningful impact on their lives at baseline.

Psychological wellbeing

At baseline, means scores on the HADS anxiety and depression subscales were within normal range[27] (i.e. not indicative of clinical anxiety or depression; reported in the trial CSRs[9,12,18,19]). The company stated that there was a "numerically greater improvement" in the HADS total score of depression and anxiety (Doc B, p.75). However, not only was this finding not statistically significant, but the 'numerical change' was well under published thresholds for a clinically meaningful change in HADS in any population[28]. The EAG therefore agreed with the assessment of the EMA that there was no difference in HADS score between those receiving ruxolitinib and vehicle cream at 24 weeks. There was also no benefit of ruxolitinib on HADS at 52-week follow-up. The company did not report change in HADS for those who reported clinically significant symptoms of anxiety and depression at baseline.

The EMA SmPC report[1] also reported no meaningful difference in outcomes on the WHO-5 (a measure of general wellbeing) between trial arms.

Subgroup analyses

Subgroup analysis of F-VASI75 presented by the company (CS Doc B, p.82) showed a differential treatment effect according to participant age (larger effect in adolescents than adults) and facial BSA at baseline (larger effect in those with greater facial vitiligo). Clinical advice to the EAG was that these findings would be expected, given that these groups tend to show better outcomes following all treatments for vitiligo. There was no difference in treatment effect between participants with Fitzpatrick scale Type 1/2 and Type 3/4/5/6.

Data for some outcomes was provided for trial participants who had previous received treatment at clarification (question C2). These data appeared to be excerpts from the appendices of the trial CSRs, though these tables were not provided to the EAG in the appendices of CSRs provided earlier in the appraisal (though these and all data tables were requested by the EAG). Within the timeframe of the appraisal, it was not possible for the EAG to review all these documents, however the EAG considered the documents that related to the primary outcome of the trials (F-VASI75). The three files for this outcome were not adequately labelled and the sample sizes reported in the tables did not clearly match the trial data to confirm identification, however the EAG assumed the following:

- File 'T_1_1_1_1_FVASI75.RTF' reports data for one of the TRuE-V1 and TRuE-V2

- File 'T_1_1_1_2_FVASI75.RTF' reports data according to whether participants received any previous treatment for the pooled TRuE-V1 and TRuE-V2 trials
- File 'T_1_1_1_3_FVASI75.RTF' reports data according to whether participants received previous TCI or TCS

The data assumed to be based on the pooled trials showed that those who had previously received treatment showed a very slight increased chance of a response to ruxolitinib compared to the broader population ([redacted] vs 30.7% at 24 weeks; [redacted] vs 51.6% at 52 weeks). The company did not report a formal subgroup analysis to compare response between those who did and did not receive previous treatment, however the EAG assumed that there would be no statistically significant difference between groups. As described in Key Issue 2, there is significant uncertainty over the data used by the company to represent the previously treated subgroup.

Adverse effects

Ruxolitinib was associated with a small increase in the risk of adverse events compared to vehicle cream. Mostly these were mild adverse events but there was an increased risk of adverse events affecting the treated area, including acne, pruritus, erythema and rash. The EAG considered that these would not contribute to major health concerns or healthcare resource use, though considered that people using ruxolitinib who experience these events may be more likely to discontinue treatment or else change the application of ruxolitinib to another area of the body. The rate of adverse events increased between the 24-week and 52-week timepoint, suggesting that new events may emerge with longer exposure.

There was also a small increase in the rate of serious adverse events in those who received ruxolitinib. The trial investigators determined that none of these events were related to treatment. Event rates were extremely low and with no obvious pattern that was suggestive of a particular risk with ruxolitinib.

Oral ruxolitinib has been associated with an increased risk of nonmelanoma skin cancer[29] (NMSC) in other skin conditions. The EAG was unclear how dosing between the topical and oral formulations of ruxolitinib compared, though the company reported no skin cancer events in the TRuE-V1 and V2 trials, or in the TRuE-V-LTE (as reported in the CS and trial CSRs). However, the SmPC[1,26] report notes that ten participants with vitiligo receiving ruxolitinib across the broader evidence base (including trials not reported in the CS) experienced a non-melanoma

skin neoplasm, most commonly (n=3) basal cell carcinoma. The SmPC for ruxolitinib[26] noted that a causal relationship with ruxolitinib has not been identified, though "4/5 patients had NMSC at an application site" (p.168) and they considered that the follow-up of the ruxolitinib trials in vitiligo was insufficient to determine whether NMSC may develop over time. The EMA, MHRA and clinical advice to the EAG concurred that people who receive treatment with ruxolitinib should be monitored for skin cancer, pending further evidence.

3.3. Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company conducted a SLR to identify relevant clinical trial evidence for the submission. The results of SLR were used to assess the feasibility of a robust indirect treatment comparison (ITC) to estimate the relative efficacy of ruxolitinib versus other therapies. A summary of this process is reported in Section B.2.9 of the CS, with more detail of the methods presented in Appendix D1.2. The population, intervention, comparator, outcomes, and study design (PICOS) criteria used in the ITC are presented in Table 12, Appendix D.

A total of 253 studies were included in the SLR and were screened for inclusion in the feasibility assessment (FA). Twenty-four potential comparator studies and four studies related to ruxolitinib cream were included in the ITC FA. The screening process was reported in Table 13 (Appendix D) but specific reasoning for excluding studies was not presented. After the feasibility assessment, the company concluded that there was an insufficient evidence base to robustly compare the efficacy of ruxolitinib to existing therapies. They reasoned that the lack of comparable studies was partly due to an evolving set of tools that were used to evaluate vitiligo. In addition, they noted that most of the clinical studies were of low methodological quality.

3.4. Additional work on clinical effectiveness undertaken by the EAG

The EAG conducted an assessment of studies included in the company's SLR that could plausibly be included in an ITC. The majority of the studies identified by the company were small, often fewer than 50 participants, and the EAG agreed that there was between-study heterogeneity in terms of study design and patient population characteristics.

However, the HI-Light Vitiligo Trial[30] was a large, placebo controlled RCT, conducted in the UK. Participants were randomised to either dummy NV-UVB plus TCS (TCS group), NV-UVB plus vehicle cream (NB-UVB group), or NV-UVB plus TCS (combination group). The NV-UVB used was a home-based handheld narrowband ultraviolet B (NB-UVB). As noted in Section 2.4, the

EAG considered that the relevant comparator for this submission was existing 2nd line treatment options, including NV-UVB with or without TCS, in line with the treatment pathway published by BAD[21]. The EAG considered that the HI-LIGHT trial was a highly relevant evaluation of treatments for NS vitiligo, and noted that the company used published evidence from the HI-Light Vitiligo Trial[30] within a multistep process to estimate patient EQ-5D-3L utility values to assign to health states in the company's economic model (see Section 4.2.8).

The EAG independently considered the feasibility of conducting an ITC to compare ruxolitinib to NV-UVB plus TCS utilising the HI-Light Vitiligo Trial. After an appraisal of the available evidence base, the EAG considered that a network meta-analysis (NMA) could potentially be conducted using Eleftheriadou 2014[31], the pilot Hi-Light trial, to connect TRuE-V1[18] and TRuE-V2[19] to the HI-Light Vitiligo Trial[3] in the analysis. The EAG also considered that the company may have been able to utilise individual patient data (IPD) from the pooled TRuE-V1 and TRuE-V2 trials to perform an unanchored matching-adjusted indirect comparison to the relevant arm in the HI-Light Vitiligo Trial. The EAG appraisal of the feasibility of these options is described in the following sections. Details of the studies considered by the EAG in its assessment, including inclusion and exclusion criteria, baseline demographic and disease characteristics, and potential outcomes are presented in Table 34 in Appendix A.

3.4.1. Network meta-analysis

The EAG assessed whether conducting an NMA utilising Eleftheriadou 2014, the pilot Hi-Light trial, to connect TRuE-V1and TRuE-V2 to the HI-Light Vitiligo Trial could produce a credible estimate of effect.

A key limitation to this approach would be the small size of Eleftheriadou 2014, the pilot Hi-Light trial. This pilot trial included 19 participants in the NB-UVB arm and 10 participants in the placebo arm. This led to treatment groups that were not well matched in terms of their baseline or disease characteristics. The EAG was also concerned that there were systematic differences in the participants recruited to the comparator trials and the ruxolitinib trials. The age, and BSA involvement inclusion criteria varied between TRuE-V1/TRuE-V2 and the comparator studies. Also, the participants recruited to the HI-Light Vitiligo Trial had more progressive disease compared to the TRuE-V1and TRuE-V2 trials, where only 175 (26%) were reported to have progressive disease. Given the limitations noted, the EAG did not consider an NMA to be a robust approach to estimate the effectiveness of ruxolitinib in comparison to NV-UVB with or without TCS.

3.4.2. Unanchored matching-adjusted indirect comparison

The EAG assessed whether performing an unanchored matching-adjusted indirect comparison (MAIC) to the combination arm in the HI-Light Vitiligo Trial could produce a credible estimate of effect.

An unanchored MAIC approach does not require the use of the small Eleftheriadou 2014 in the analysis. It would allow for the analysis to be adjusted to match variation in baseline characteristics reported in the HI-Light Vitiligo Trial, and for which TRuE-V1/TRuE-V2 has IPD. The EAG noted that there were baseline characteristics not reported in the HI-Light Vitiligo Trial that cannot be matched utilising this analysis. This included disease status and mean T-BSA (% of the total body involved). This is in addition to the limitation inherent to all MAICs that despite the use of IPD to reduce observed cross-trial differences, unobserved differences may result in residual confounding.

The principal limitation of using unanchored MAIC for this analysis was variations in the outcomes reported in the trials. The primary outcome reported in the TRuE-V1/TRuE-V2 trials was F-VASI75, which constitutes an improvement of at least 75% from baseline in the F-VASI. The company also reported T-VASI75, which constitutes an improvement of at least 75% from baseline in the T-VASI. The repigmentation outcome reported in the HI-Light Vitiligo Trial is > 75% repigmentation using digital images taken at baseline and at 9 months of a single “target patch” per person. This target patch has “active” vitiligo and is therefore new or has changed over the past 12 months.

The EAG’s clinical expert noted that VASI measures depigmentation on the whole body (T-VASI) or the whole face (F-VASI). Thus, it is a global measure of repigmentation rather than targeting a single active patch and it could include patches that are stable and patches that are progressive. The EAG noted that the target patch was active and therefore more likely to be classed as progressive. The EAG’s clinical expert confirmed that active patches were thought to be more responsive to treatment.

Given substantial differences between the outcomes reported in the TRuE-V trials and the HI-Light Vitiligo Trial, the EAG did not consider an unanchored MAIC to be a robust approach to estimate the effectiveness of ruxolitinib in comparison to NB-UVB plus TCS.

3.5. Conclusions of the clinical effectiveness section

Overall, the EAG considered that the presentation of clinical effectiveness data in the CS was poor and lacked transparency, which prevented a full appraisal of the clinical effectiveness of ruxolitinib. The EAG was particularly concerned about the omission of clinical effectiveness evidence in the population subgroup that was used in the company's economic model (previously treated) and the omission of several completed trials of ruxolitinib from the CS. From the evidence appraised by the EAG, the EAG considered that:

- A significant minority of people in the clinical trials showed a clinically meaningful response in facial vitiligo with ruxolitinib over and above vehicle cream. This response was above the threshold considered by the EAG's clinical expert to be meaningful for people with vitiligo. Vitiligo patches on the face are particularly distressing for people with vitiligo, and the EAG considered that the improvements in facial vitiligo for these participants would be meaningful to them.

- The treatment effect of ruxolitinib for total vitiligo was lesser than that of facial vitiligo, with fewer participants showing a response in TVASI. The EAG was unable to explain the reduced efficacy for TVASI and considered there to be no evidence that the treatment response for bodily vitiligo would be slower to emerge. While the licence for ruxolitinib was limited to people with vitiligo affecting the face, there was no restriction on where people who receive ruxolitinib can apply the cream (up to 10% of BSA). As vitiligo affecting the face was one of the symptoms that people with vitiligo reported to be most distressing, the EAG considered it reasonable to assume that most people with facial vitiligo would apply the cream to their faces. However, the EAG noted that variation in the location of the cream may affect the clinical benefits experienced.

- The effect of ruxolitinib increases over time, with some variation across people in the speed and magnitude of response experienced. Clinical advice to the EAG was that dermatologists will typically continue treatments for vitiligo when people show >20% pigmentation change every 3-4 months. As more than half of people treated with ruxolitinib did not show a clinically meaningful response as compared to vehicle cream, the EAG considered that a strategy to allow a response to develop while discontinuing those who will not experience a treatment benefit would be optimal for prescribing ruxolitinib.

- Trial participants did not show overall benefits of ruxolitinib for HRQoL or psychological wellbeing. The EAG considered it plausible that people who experienced significant improvements in their vitiligo may experience a meaningful benefit in these outcomes, but these data were not presented by the company.

- Ruxolitinib appeared to be associated with a low risk of adverse events, with the most common adverse events being mild in nature. Nevertheless, the EAG considered that the types of adverse events reported may affect treatment use; for example, people may choose not to apply ruxolitinib to their face if they experience acne, and this in turn may affect treatment efficacy.

- The EAG considered that the effectiveness of ruxolitinib in the subgroup of people who had previously received treatment was uncertain. The EAG had no evidence to believe that treatment effects would be different in those who had previously received treatment, however considered that an appraisal of these data would be useful to reduce this uncertainty.

- The relative effectiveness of ruxolitinib as compared to other treatments for vitiligo was an ongoing source of uncertainty in the appraisal. Following an appraisal of the evidence base identified in the company's SLR, the EAG agreed with the company's conclusion that a statistical comparison of ruxolitinib with relevant 2nd line treatment options using either an NMA or a MAIC was not feasible and/or would not be useful for decision-making. A naïve comparison of clinical outcomes between people who received ruxolitinib in the TRuE-V trials and outcomes reported in a large, UK based trial[30] of NB-UVB therapy and combination TCS and NB-UVB therapy suggested that more people may respond to ruxolitinib than either of the other treatments. However, without a head-to-head comparison, any conclusions about the relative effectiveness of ruxolitinib would be highly uncertain.

4. COST-EFFECTIVENESS

4.1. EAG comment on company's review of cost-effectiveness evidence

The company conducted a SLR of previous economic evaluations, the searches for which were considered well-structured and executed using a good range of sources. However, as stated in CS B.3.1, the company did not use the findings from their SLR to inform their economic model structure. The company applied a different filter to results from the same search to identify resource use and cost evidence but did not report in CS B.3.5 if or how the SLR was used to inform cost and resource use data selection and assumptions. Similarly, in CS B.3.4, the company reported conducting a SLR of health-related quality of life evidence, but it was not clear the extent to which and how the findings from this review informed the company's approach to patient utility assumptions, aside from a key mapping study being identified outside of the SLR, as noted in section 4.2.8 of this report. The EAG noted that in the company's HRQoL SLR, case reports and conference abstracts were excluded. It would be better practice not to use a 'study type' filter for these searches and to use a utilities filter instead; it was possible that some relevant data may have been missed as a result, if it was in a paper reporting a different type of study not included in the filter.

4.2. Summary and critique of company's submitted economic evaluation by the EAG

4.2.1. NICE reference case checklist

Table 17: NICE reference case checklist

Attribute	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	✓ No comment
Perspective on costs	NHS and PSS	✓ No comment
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	✓ No comment
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The company's lifetime horizon may be considered sufficient but excessive, in the context of a treatment that neither extends survival nor offers expected

		long-term health benefits after treatment cessation
Synthesis of evidence on health effects	Based on systematic review	The company reported conducting relevant SLRs but it was not clear how these reviews informed data selection and synthesis choices in the company's analysis
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Health effects were expressed in QALYs. EQ-5D data were not collected in the TRuE-V trials. In section 4.2.8 the EAG explains and critiques the company's multi-step and multi-source approach to measure and value health effects
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	HRQoL data collected in the TRuE-V trials were not used in the company's multi-step and multi-source approach to measure and value health effects
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Relevant preference data were used within the company's multi-step and multi-source approach to measure and value health effects, as explained in section 4.2.8
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	✓ No comment
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	✓ No comment
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	✓ No comment

Key: EQ-5D, EuroQol 5 dimension; HRQoL: health-related quality of life; NHS, National Health Service; PSS, Pseronal Social Services; QALY: quality-adjusted life year; TA: technology appraisal

4.2.2. Validation

Upon receiving the company's model, internal checks were performed to ensure that the flow of patients and calculations behaved as intended. These included simple validity checks, the

assessment of cost and clinical inputs and review of Microsoft Excel® spreadsheet and Visual Basic for Applications® logic.

The submitted model passed standard internal consistency and stress checks performed by the EAG. However, sheet-by-sheet EAG review of the company model revealed clear issues with logic applied in the analysis, documented in section 4.2.5. Clinical inputs including patient characteristics, response status, the probability of treatment discontinuation and rates of adverse events were pooled across the TRuE-V studies. The EAG noted an error in the numerator of the 'no regain response' calculation, which related to miscategorising missing data entries as responses, covered in section 4.2.7.

Cost references were deemed suitable if taken from the most up-to-date sources relevant to the perspective of the National Health Service (NHS) and personal social services (PSS). Section 6.1 explains any amendments made to cost inputs provided by the company, using either drug costs within the company's provided appendix, or from the NHS Drugs and pharmaceutical electronic market information tool (eMIT) if less expensive.

4.2.3. Population

The company reported MHRA marketing authorisation for ruxolitinib to treat NSV with facial involvement in adults and adolescents aged 12 years and older, consistent with the TRuE-V1 and TRuE-V2 study populations informing the license. The final NICE scope listed no subgroups of interest. The British Association of Dermatology's professional organisation submission expressed a need for ruxolitinib early in the treatment pathway: "*Due to the lack of licensed treatments for vitiligo, and the fact that usually first line treatment for vitiligo includes topical preparations (TCS or TCI), ruxolitinib would fit into the first line treatment category alongside TCS and TCI and perhaps following a short trial of TCS or TCI*". Nevertheless, the company's economic analysis considered a subgroup of the licensed population, for whom a NICE recommendation is being sought: people aged 12 years and older for whom first-line topical treatments (TCS or TCI) are not suitable. Specifically, "*patients whose disease has not responded to TCS or TCI, or for whom TCS or TCI are contraindicated, not tolerated or otherwise medically inadvisable*". Clinical advice to the EAG was that this was a reasonable potential position for ruxolitinib, given ease of access to TCS and TCIs, and that a reasonable minority of people with vitiligo respond to these treatments. In clinical practice, the EAG's adviser noted that TCSs are typically tried first. If this does not work, tacrolimus (TCI) would be the next option to consider, or possibly TCS under occlusion. After exhausting topical treatment

options, NB-UVB and other second-line treatment options would be considered. The EAG's adviser considered that ruxolitinib could be used after other topical treatments had been exhausted, but before NB-UVB and other second-line treatment options were considered.

In the economic analysis, the company labelled the population of interest the "prior therapy" population. From the company's August 2023 original evidence submission, "prior therapy" did not appear to be a prespecified subgroup of the TRuE-V1 and TRuE-V2 trials, as discussed in Section 3. TCS or TCI exposure or suitability was a factor neither in the analysis populations tabulated in section 5.1 of the TRuE-V1 CSR, nor in the subgroups listed in section 9.5 of the same document. As such, the precise definition of the "prior therapy" subgroup whose data informed many elements of the economic analysis was not explicitly clear. What was more easily inferred was that the "prior therapy" subgroup did not cover all patients in the marketing authorisation; those who have not previously received therapy but for whom TCS or TCI are contraindicated or medically inadvisable are not represented. The EAG were unclear on the generalisability implications of this issue and noted it as an area of uncertainty for decision-making. This issue is captured by Key Issue 2.

"Prior therapy" subgroup data naïvely pooled across TRuE-V1 and TRuE-V2 samples informed baseline age, weight and gender characteristics in the economic analysis. These characteristics partially informed patient utility and treatment cost assumptions as described in 4.2.8 and 4.2.9. Pooled "prior therapy" TRuE-V1 and TRuE-V2 outcomes data informed treatment effectiveness and patient utility assumptions, as described in 4.2.7 and 4.2.8. Pooled TRuE-V1 and TRuE-V2 ITT data and estimates from the wider literature are used as proxy data in some instances, as noted throughout 4.2.7 to 4.2.9.

4.2.4. Interventions and comparators

The intervention in the company's analysis was ruxolitinib 1.5% cream, self-administered. The recommended dose is a thin layer of cream applied twice daily to the depigmented skin areas up to a maximum of 10% of BSA[1]. Clearly, the dose will vary by patient, based on varying extent of depigmentation and BSA across patients, varying interpretations of "thin layer" and "10% of BSA" across patients, and varying adherence to recommendations across patients. Based on clinical advice to the EAG, the dose used in practice may also vary depending on which areas of skin are considered the most important to patients. The SmPC and Information for patients leaflet each stated that no more than two 100g tubes per month should be used[1].

The company's analysis assumed that exactly 4.03g ruxolitinib was applied per day, which the company reported was the "*TRuE-V pooled median weight of study drug applied daily during 24-week period*", across ruxolitinib and vehicle cream arms. The EAG had several concerns with this approach to ruxolitinib dose calculation, all of which were agreed with clinical expert advice:

1. Overarching more specific concerns, uncertainty around the amount of ruxolitinib used in practice was important for expected cost-effectiveness results.
2. The EAG considered the use of vehicle cream dosing data in combination with ruxolitinib dosing data to estimate expected ruxolitinib dosing data to be inappropriate, when ruxolitinib dosing data could be used in isolation.
3. The EAG was concerned that in practice, with less medical oversight than in a trial setting, patients may be inclined to use more ruxolitinib, whether that means applying ruxolitinib more thickly or across more skin surface area. Patients may in practice have in mind the stated limit of two tubes a month. This equates to 6.57g (2dp) per day, [redacted]% (2dp) more than the daily dose assumed by the company.
4. The EAG was mindful that wastage; caused for example by accidently squeezing to excess, or by loss or mis-storage of the tube; may be more likely in practice than in a trial setting.
5. The EAG was conscious that patients would be issued 100mg tubes, and that any unused medicine in an open tube at the point of discontinuation would be wasted.

   Though not mentioned in the CS, the ruxolitinib tube sizes in TRuE-V studies were different to those that would be available in practice. In addition, maximum recommended use was higher in the TRuE-V studies than was advised in the UK label. The published protocol[32] for the TRuE-V studies stated that ruxolitinib was provided to patients in 60g tubes, and that participants were advised to limit use to no more than one 60g tube every week; 240g every 28 days.
6. The EAG was concerned that prescribing practice may tend towards the two 100mg tubes per month limit, even if patient use does not. For example, some patients may use less than two tubes each month but be prescribed two tubes per month nonetheless. The EAG's clinical adviser suggested that the company might consider producing smaller tubes. The EAG noted that the company produced 60g tubes for use in TRuE-V studies (point 5).

To partially address the first and second of these concerns, the EAG asked the company to provide further trial dosing data as a priority EAG question (B10). In response, the company stated that it was not possible to provide anonymised patient-level dosing data during the time available but did provide further summary data that shed further light on dosing differences across and within trial arms. These data are partially reproduced in Table 18, below.

Table 18: TRuE-V1[18] and TRuE-V2[19] ruxolitinib exposure summary statistics, adapted from Tables 6 and 7 of the company's response to EAG Clarification Q B10.

Variable	Ruxolitinib 1.5% Cream BID – TRuE-V1		Ruxolitinib 1.5% Cream BID – TRuE-V2	
Average weight of study drug applied daily	***During the double-blind period (g)***	***From Day 1 to Week 52 (g)***	***During the double-blind period (g)***	***From Day 1 to Week 52 (g)***
N	221	[redacted]	228	[redacted]
Mean (s.d.)	5.82 (16.587)	[redacted]	8.86 (31.385)	[redacted]
Median	4.17	[redacted]	3.96	[redacted]
Min, max	0.4, 237.1	[redacted]	0.4, 237.0	[redacted]

Abbreviations: BID, twice daily; s.d., standard deviation

Table 18 shows summary statistics for daily weight of ruxolitinib used across TRuE-V studies[18,19], stratified by study and timeframe from baseline. These data allow a focus on ruxolitinib data only, to estimate expected ruxolitinib doses, addressing the second of the EAG's initial concerns. In terms of the distribution of the data, the data were clearly skewed to the right: mean daily ruxolitinib use was notably higher than median daily ruxolitinib use, across studies, in the double-blind period [redacted]. The standard deviation and minimum and maximum statistics in Table 18 further clarify the distribution of drug use across the study samples. The data indicated that some TRuE-V patients used more ruxolitinib than was recommended in the license wording. As noted above, two 100mg tubes a month equates to 6.57g (2dp) per day; less than the mean daily use in TRuE-V2 in the double-blind period [redacted].

The implication of uncertainty around dosing in the TRuE-V studies[18,19] and of expected ruxolitinib use in practice upon cost-effectiveness estimated are explored in section 6 of this report, though the EAG's clinical expert has reassured the EAG to an extent on some of these potential issues. Without a strong position on expected ruxolitinib use in practice, the EAG's expert noted that it may be the case that patients become less adherent as time goes on, and the burden of two applications per day, alongside other skin applications many vitiligo patients

use, may lead to less use than recommended. On the other hand, as shown in Table 18, in TRuE-V1 and TRuE-V1, [redacted]

As described and critiqued in section 2.4 of this report, the company proposed vehicle cream, the control treatment in TRuE-V1 and TRuE-V2 trials, as the sole relevant comparator for their proposed positioning. As detailed in 2.4, the EAG was not convinced by this proposition. In short, vehicle cream was, by definition, not expected to have any effect in isolation. As such, vehicle cream was not part of the treatment pathway as described by BAD guidelines[21] and summarised in 2.3. Given the company's proposed positioning, EAG clarification question B1 (marked "Priority") asked the company to respecify the cost-effectiveness comparison at an appropriate point in the treatment pathway, with appropriate comparators. As documented in section 2.4 of this report, the company declined to do so.

Submissions from Vitiligo Support UK and BAD, supplemented by conversation with the EAG's clinical expert; an author of the BAD submission; have helped clarify the treatment landscape for the EAG, as discussed in Section 2. While the BAD treatment pathway in Figure 4 of the CS reflected the active treatment pathway for the relevant patient population, it became clear to the EAG that many vitiligo patients become lost to the system, owing primarily to system delays and the patient burden of some treatment options. In the first instance, GP prescription of topical first-line treatment may not be continued sufficiently long enough for a full treatment effect to manifest, which may lead to patient disengagement. Referral to secondary care is typically long and can involve a wait of up to a year. Once accessed, topical treatments (TCS and/or TCIs) may be tried again or for the first time under dermatologist direction, before NB-UVB is recommended for most patients (alone or in combination with topical treatments). However, NB-UVB is burdensome for the patient in requiring presentation at the secondary care centre two to three times a week. For some patients, for example adolescents in secondary education, this is not feasible. Patients can become disengaged at any point of the treatment pathway.

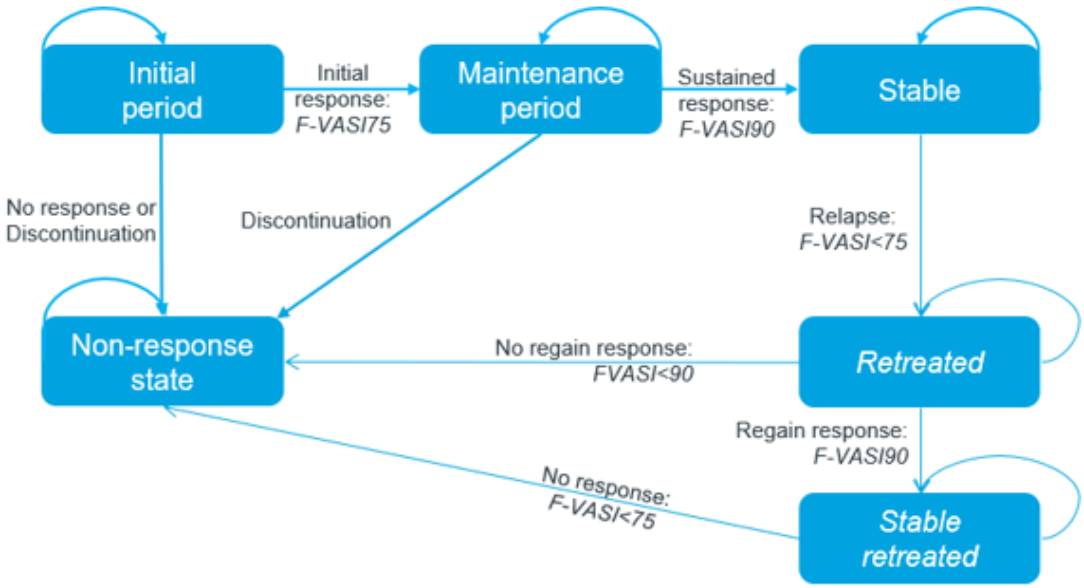
As such, it was the EAG's view that vehicle cream could be considered an appropriate proxy comparator for no treatment, at the end of the treatment pathway. This was inconsistent with the company's proposed positioning of ruxolitinib into the secondary care setting as an option after current 1st line treatment options (i.e., when other topical treatments have either been tried or are otherwise inappropriate). In this setting, the EAG's clinical advisor was clear; a dermatologist would try another option. The introduction of ruxolitinib here would displace,

delay, or add to the second-line BAD-recommended treatment options: NB-UVB with or without topical TCS or TCI, or for patients with progressive disease, betamethasone with NB-UVB.

4.2.5. Model structure and logic

The company's economic analysis comprised a *de novo* cohort-level model built in Microsoft Excel®; the company's model schematic is reproduced in Figure 5, below. Movements between states were allowed every 4 weeks. General population mortality data were used to capture the probability of death in each cycle; vitiligo was assumed to have no effect upon mortality, and no health state in the company's model was associated with a higher or lower chance of death than another.

Figure 5: Company's model structure schematic (CS Figure 20)



Note: Dead, not presented in the figure for simplicity, is an absorbing state and can be reached from any of the other health states

Identical model cohorts across (i) ruxolitinib and (ii) vehicle cream arms of the analysis entered the model in the "Initial period" state. Patients could discontinue into the "Non-response" state at the end of any of the initial model cycles, or otherwise either discontinue or continue into the "Maintenance period" state at the end of the "Initial period", based on whether or not F-VASI75 had been achieved. The CS reported the "Initial period" to end at 24 weeks, in line with the timing of the primary endpoint assessment in TRuE-V1[18] and TRuE-V2[19] However, this was not the case in the company's model, for two seemingly unintended reasons. First, the company

used a half-cycle correction, implying health state transitions at the mid-point of each 4-week cycle. Second, the initial period in the company's analysis lasted seven 4-weekly cycles, not six.

The EAG were mindful of clinical advice that F-VASI was not a measure used routinely in clinical practice, owing to its time-intensive nature. However, advice to EAG also noted that it is a robust and appropriate registrational trial measure, and that in aiming to capture repigmentation it is similar in its intentions to the more rudimentary measurements used in clinical practice. Perhaps more consequentially, the assumption that patients would discontinue owing to lack of efficacy if they have not achieved F-VASI75 at 24 weeks (the primary endpoint in TRuE-V1[18] and TRuE-V2[19]) was not in line with current NHS clinical practice. It was also not in line with the TRuE-V trials, in which all patients could receive ruxolitinib from week 24 to week 52, during the open-label extension period. The EAG's clinical advisor explained that they would assess a patient every 3-4 months and look for around 20% improvement at each visit to justify treatment continuation (i.e., a seemingly lower threshold of response is sought in practice, versus what is proposed by the company in its model). The SmPC states: "*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.*".[1] As such, in assuming all patients who have not achieved F-VASI75 at 24 weeks would discontinue to a non-response state, the company underestimated the proportion of patients who would continue treatment (and continue to accumulate treatment-related health benefits and costs) after 24 weeks if current practice for determining treatment continuation remains unchanged. This issue is compounded by the company's structural assumption that patients who enter the non-response state cannot move to another alive state. The non-response state is the state the company assumed was associated with the lowest patient utility and the second highest cost (after those in which ruxolitinib treatment costs are incurred), as described and critiqued in sections 4.2.8 and 4.2.9, respectively. Clinical advice to the EAG was clear: a consultant dermatologist would look to another treatment option after topical treatment.

After the "Initial period", the company assumed that those who were routed to maintain treatment remain in the "Maintenance period" state unless they discontinued treatment or died, until the cycle starting at week 56 (though the company reported this occurring at week 52, in line with the end of the TRuE-V open label extension period). The company's analysis assumed a time-invariant monthly discontinuation probability in the maintenance period that is distinct from that of the "Initial period". The data and assumptions informing the company's approach to discontinuation are described and critiqued in greater detail in section 4.2.7.

Though it is not represented in Figure 5, the company partitioned the “Maintenance period” state by response status; F-VASI75-89 versus F-VASI≥90; which allowed different utility assumptions to be applied for these two groups. However, this partitioning led the company to make structural assumptions that were unexplained in the CS and seemed to be unintentional and illogical. For example, it was structurally impossible for a patient in the “Maintenance period” state with F-VASI75-89 to achieve F-VASI≥90 and therefore transition to the “Stable” state; from “Maintenance period” state with F-VASI75-89, it was only possible to move to “No response” or death. Further, the company implied in the CS (B.3.2.2) that sustained response was defined by achieving F-VASI≥90 after the TRuE-V open-label extension phase, and that achieving sustained response should trigger moving onto the “Stable disease” state, where treatment was no longer needed. Yet, in the analysis, a cycle probability of sustained response (calculated from TRuE-V pooled data as described in section 4.2.7) was multiplied by the at-risk membership of the “Maintenance” F-VASI≥90 partitioned state. The company’s description of sustained response would suggest that the full at-risk membership of the “Maintenance” F-VASI≥90 partitioned state should transition to the “Stable disease” state for the next model cycle, after the TRuE-V open-label extension phase. In short, the EAG was concerned that the company had not modelled transitions from the “Maintenance period” to “Stable disease” as intended or stated.

In the “Stable disease” state, it was assumed that only disease management costs were incurred. There was no other state with higher assumed patient utility or lower assumed healthcare costs, as described and critiqued in sections 4.2.8 and 4.2.9. As illustrated in Figure 5, with the exception of moving to ‘dead’, it was only possible to move from “Stable disease” to “Retreated” (i.e., ultimately, all surviving patients would eventually move to re-treated provided the model time horizon was long enough). This occurred based on a time-invariant cycle probability of F-VASI <75, as detailed in section 4.2.7. It was an intentional structural limitation of the company’s model that movements from “Stable disease” to “Non-response” were not possible. The company assumed that retreatment was with the same topical treatment as used previously. On the intervention arm, this meant retreatment with ruxolitinib. Expert advice to the EAG suggested that retreatment with ruxolitinib would be rational, if near complete repigmentation was achieved, prompting discontinuation, which then led to depigmentation. On the comparator arm of the company’s analysis, this meant retreatment with vehicle cream. This was clearly not a reflection of clinical practice.

From “Retreated”, it was possible to transition to “Stable retreated”; which was equivalent to “Stable” in its cost and patient utility assumptions; or to the non-response state. The probability of transitioning to each of these states, and of transitioning to non-response from “Stable retreated”**,** was determined by F-VASI. It was assumed that there was no chance of discontinuing treatment for reasons other than the achievement of stability or loss of efficacy.

Eventually, the distribution of alive patients in the company’s analysis tended towards the non-response state, as indicated by Figure 5. In the company’s base case, this manifested as 95% of the cohort being in either “Non-response” or dead by around 8.5 years. As noted above, the non-response state was assumed to be associated with a high cost and low patient utility. The high assumed cost was driven primarily by the assumption that patients in this state incurred a monthly “Hospital-based NB-UVB” cost of £643.24 as described in section 4.2.9. Clinical advice to the EAG suggested that in practice, patients in long-term non-response would be likely to become disengaged with the healthcare system, with unmet need and low healthcare costs. It seemed that the company had received similar advice, but looked to reflect this in the model by assuming that all non-response health state costs discontinue after exactly 10 years: “*Disease management costs in the non-response health state are assumed to apply for the first 10 years only since the start of model simulation following input from clinical experts who stated that patients would consider discontinuing treatment and visits to the healthcare specialists after a certain period without any improvement*” (CS, p130). The company’s decision to select a 10-years-from-baseline time point, which was not linked to the duration of time any response to treatment was achieved, was not substantiated.

Overall, the EAG registered a range of concerns with the company’s model structure and logic, both with the company’s intended model design and its limited reflection of the EAG’s understanding of the vitiligo treatment pathway in NHS England practice, and, in places, with the rationale of logic in the company’s model, given the CS description of intentional design.

4.2.6. Perspective, time horizon and discounting

The perspective of the company’s analysis was that of the NHS and PSS on costs and that of patients on health effects, in line with the NICE reference case [33]. The company discounted cost and health outcomes at 3.5% per annum, also in line with the NICE reference case.

The perspective of the company’s analysis was lifetime. In the base case deterministic analysis, the mean age of the “prior therapy” subgroup (37.8 years) was assumed for the cohort at

baseline. The model's time horizon was set to 64 years, taking this cohort to age 101.8 years by the end of the time horizon. A lifetime horizon was sufficient but excessive, in the context of a treatment that neither extends survival nor offers expected long-term health benefits after treatment cessation.

Figure 6, produced by the EAG within the company's model, illustrates how the ICER produced by the company's list price deterministic base case analysis changed as the model's time horizon was varied from 5 to 64 years.[*] The figure shows that calculations beyond a 30-year time horizon had little impact upon the headline deterministic result. The figure also illustrates how the ICER fell as the time horizon increased from 5 years to 10 years, then increased at a decreasing rate as the time horizon increased beyond 10 years. The reason for the 10-year pivot in Figure 6 is the company assumption; discussed and critiqued in Section 4.2.5; that costs in the "non-response" state ceased to occur after exactly 10 years from model entry.

Figure 6: Relationship between model time horizon and company's list price base case deterministic ICER

Abbreviations: ICER, incremental cost-effectiveness ratio.

[*] To reduce the time horizon to 5 years, the EAG had to override data validation settings. This analysis was purely intended to demonstrate the relationship between the ICER and the time horizon in the company's model.

4.2.7. Treatment effectiveness and extrapolation

Broadly, the transition probability estimates governing movements between the model health states in Figure 5, as described and critiqued in Section 4.2.5, were based on a combination of summary TRuE-V1[18], TRuE-V2[19] and TRuE-LTE[9] data and assumptions. Table 33 of the CS was set out as summarising the key trial data and assumptions applied in the company's analysis, and is reproduced below as Table 19 for reference.

Table 19. Key TRuE-V1[18], TRuE-V2[19] and TRuE-LTE[9] data and assumptions applied in the company's analysis (CS Table 33)

Response category	Ruxolitinib cream		Vehicle cream		Section	Source
	Efficacy	SE	Efficacy	SE		
Initial and sustained response						
Initial response (F-VASI75 at week 24)*	[redacted]	[redacted]	[redacted]	[redacted]	Section B.3.3.3.1	Derived from pooled results of TRuE-V1 and TRuE-V2 data (Phase III) [26]
Sustained response F-VASI90 at week 52	[redacted]	[redacted]	Equal treatment effect assumed		Section B.3.3.3.2	
Relapse						
Time to relapse data (i.e., time to F-VASI<75) at week 104	Equal treatment effect assumed		[redacted]	[redacted]	Section B.3.3.3.3	Derived from Cohort A TRuE-V LTE (Phase III) [18]
Retreatment						
Regain response (F-VASI90 at week 104)	Equal treatment effect assumed		[redacted]	[redacted]	Section B.3.3.3.4	Derived from Cohort A TRuE-V LTE (Phase III) [18]
No regain response (F-VASI<75 at week 52 and F-VASI<90 at week 104)	[redacted]	[redacted]	Equal treatment effect assumed		Section B.3.3.3.4	Derived from Cohort B TRuE-V LTE (Phase III) [18]
Loss of response following retreatment (stable retreated)	Equal treatment effect assumed	[redacted]	Equal treatment effect assumed		Section B.3.3.3.4	Derived from Cohort A TRuE-V LTE (Phase III) [18]
Discontinuation						

Response category	Ruxolitinib cream		Vehicle cream		Section	Source
	Efficacy	SE	Efficacy	SE		
Initial period	[redacted]	[redacted]	[redacted]	[redacted]	Section B.3.3.6	Derived from pooled results of TRuE-V1 and TRuE-V2 data (Phase III) [26]
Maintenance period	[redacted]	[redacted]	[redacted]	[redacted]	Section B.3.3.6	

Notes: *Initial response is broken down into mutually exclusive FVASI75-89 and FVASI90 categories for modelling purposes. ** No regain response was calculated using the simple average of two approaches to missing data (removing missing data and treating missing data as non-responders). Data presented in this table has been derived from pooled results of the TRuE-V studies and/or TRuE-V LTE. These data are presented in Appendix M.

Abbreviations: F-VASI, facial vitiligo area scoring index; F-VASI75, 75% or greater improvement from baseline in F-VASI; F-VASI90, 90% or greater improvement from baseline in F-VASI; NR, Not reported; SE, standard error.

As described in Section 4.2.5, key problems with the application of TRuE-V data lay in the discord between efficacy endpoints in the regulatory studies and the EAG's understanding of effectiveness definitions in clinical practice. The data in Table 19, above, illustrate the scale of potential discord. For example, though it is not clear from Table 19, [redacted]% of the ruxolitinib arm of the pooled TRuE-V Prior Therapy subgroup achieved F-VASI75-89 and [redacted]% achieved F-VASI90 after 24-weeks' of treatment. All remaining ruxolitinib patients (100% - ([redacted]% + [redacted]%) = [redacted]%) were assumed to discontinue "Non-response" in perpetuity at the end of the model's 'Initial period', owing to lack of efficacy. This included [redacted]% of patients who achieved F-VASI50-74, as reported in the company's model. That is, patients who achieved a 50-74% F-VASI improvement after 24 weeks of ruxolitinib were assumed to be discontinued and consigned to interminable non-response. Given clinical advice received, the EAG considered that this may lack face validity.

The reporting in Table 19 was confusing and somewhat misleading for a number of reasons, but perhaps cardinally in its misreporting of the data presented. For example, the entries in the "Loss of response following retreatment" row of Table 19 are clearly erroneous in places, indicative of a copy-paste error.

Elsewhere, what Table 19 shows as a "No regain response" estimate was applied in the analysis as a 4-week (model cycle) probability estimate. For this input, the way the company accounted for missing data in their calculations was erroneous. On p120 of the CS, the company wrote:

"Two methods to account for these missing data were used in the analysis: firstly, removing missing data from the overall sample of those with F-VASI<75 at week 52 (n=99) and secondly, treating missing data as non-responders.

"For the first method, the probability of having F-VASI<90 at week 104 if patients with F-VASI<75 at week 52 is calculated as [redacted]% ([redacted]); for the second method the probability is [redacted]% ([redacted]). In the base case, a simple average of the two methods is applied, giving an overall probability of [redacted]%."

The first method assumed that non-responders were missing at random, a strong assumption applied without sufficient evidence, but applied correctly. The second method did not treat missing data as non-response data, as described by the company. Instead, the approach miscategorised the n=[redacted] missing data entries as responses. If instead these entries had been categorised as non-response entries, the probability of non-response would have been calculated as ([redacted]+[redacted]) / [redacted] = [redacted] / [redacted] = [redacted]% (2dp). The EAG considered it more appropriate to assume that missing data were indicative of non-response than missing-at-random, and favoured this choice over the simple average of the two favoured by the company.

Part of the simplicity of the company's approach to treatment effectiveness and extrapolation was the time-invariant nature of transition probability assumptions applied. In a cohort-level Markovian model such as the company's, applying time-varying probabilities can be cumbersome, but applying time-varying probabilities that vary only from baseline is not. The company's approach to time to discontinuation assumptions, using data shown in Table 19, was a clear example of assuming time-invariance when assuming time variance may be appropriate given the data, meaningful for results, and uncomplicated to apply in the economic analysis. As such the EAG requested TRuE-V1 and TRuE-V2 Kaplan-Meier time to treatment discontinuation data, stratified by study and treatment arm, for relevant TRuE-V1 and TRuE-V2 populations, as part of EAG clarification question B8. In response, the company provided Kaplan-Meier data as requested, though without reporting censor points. A summary image of treatment discontinuation projections for the "Prior Therapy" population provided as part of this response is reproduced as Figure 7, below.

In a separate part of clarification question B8, the EAG also requested that the company use these data to incorporate functionality into the revised model to allow time-to-treatment discontinuation to be accurately modelled. The company did not do this. In light of the ruxolitinib data in Figure 7, the EAG were not overly concerned by the assumption of time-invariant

treatment discontinuation in the analysis, though more accurate use of the available treatment discontinuation data would have been preferred in the first instance. What was of more concern was how closely the company's model reflected the use of ruxolitinib in the TRuE-V open-label extension periods. As indicated in Figure 7, around 80% of patients randomised to ruxolitinib were still receiving ruxolitinib a year into treatment, and six months into the open-label extension. In the company's analysis, less than 25% of patients in the ruxolitinib arm were modelled as remaining on maintenance treatment at 1 year. Clinical advice to the EAG was noncommittal on expected length of treatment, beyond the expectation of noticeable improvements every 3-4 months justifying treatment continuation and anecdotal consideration that the burden of treatment application may take its toll months and years into treatment. In short, with respect to treatment discontinuation assumptions, the company's analysis was neither reflective of evidence from its own registrational studies nor expected clinical practice.

Figure 7: Kaplan-Meier treatment discontinuation projections stratified by TRuE study and treatment arm, as presented by the company in response to EAG clarification question B8.

Overall, the EAG considered the company's methods to incorporate data from the TRuE-V studies into the model to be subject to a number of substantial limitations. Ultimately, this meant that the EAG had little confidence in the results of the model. These issues were an overarching concern to the EAG, and in combination with concerns with the company's model structure and logic detailed in Section 4.2.5, comprised Key Issue 3. Until resolved, this prevented the EAG from presenting more than a tentative preferred base case, as discussed in Section 6.

4.2.8. Health-related quality of life

Within the TRuE-V studies, EQ-5D data were not collected. Data from other health-related quality of life measures were collected, including DLQI and VitiQoL instruments, as described in Section 3.2.2.5. Outside of the TRuE-V[18,19] studies, the company identified 24 studies investigating the HRQoL of people with vitiligo in a SLR of HRQoL evidence. However, the company did not use any TRuE-V DLQI data to inform utility assumptions in their model, nor any VitiQoL data collected beyond baseline. Furthermore, the company did not use data from any of the 24 studies identified in their SLR.

Instead, the company used an opaque and loosely justified approach to derive health state utility values that involved using F-VASI results from TRuE-V1 and TRuE-V2 in combination with a published mapping algorithm and various assumptions. To understand exactly how these utility values were generated, the EAG interpreted company reporting across (i) the appropriate section of the CS, (ii) Appendix O of the CS, (iii) a technical report embedded within Appendix O of the CS, (iv) Appendix I of the technical report embedded within Appendix O of the CS, and (v) protocols and Excel files containing regression analysis results embedded within Appendix I of this technical report. Following this, the EAG confirmed the accuracy of the EAG's interpretation of the company's multistep approach in clarification question B13. The confirmed company approach and its implicit assumptions are as follows.

1. A mapping study provided a means of generating UK vitiligo patient EQ-5D-5L utility values from RPS, VNS and VitiQoL data was identified outside of the company's systematic review[30]. In this study, Begum et al. estimated mapping algorithms using data on this range of outcomes from the HI-Light study[3]. Begum et al. also reported algorithms allowing prediction of EQ-5D-3L utility from RPS, VNS and VitiQoL data, using the Hernandez et al[34] crosswalk recommended in the NICE Manual[35].

7. Assuming RPS score was a suitable proxy for F-VASI score, the Begum et al.-reported algorithm to predict EQ-5D-3L utility from RPS data was used in combination with patient-

level F-VASI data from the Prior Therapy TRuE-V sample to generate post-baseline proxy patient-level EQ-5D-3L utility estimates for said TRuE-V patient sample.

That is, the following equation as reported by Begum et al.

$EQ\text{-}5D_{RPS} = 0.709 + (0.0119 * \mathbf{RPS}) - (0.000214 * \mathbf{RPS}^2) + (0.00000118 * \mathbf{RPS}^3)$

was interpreted as equivalent to the following as reported in B.3.4.3 of the CS, where F-VASI Category and RPS are taken as interchangeable:

$EQ\text{-}5D_{F\text{-}VASI} = 0.709 + (0.0119 * \mathbf{F\text{-}VASI\ Category}) - (0.000214 * \mathbf{F\text{-}VASI\ Category}^2) + (0.00000118 * \mathbf{F\text{-}VASI\ Category}^3)$

8. As both F-VASI and RPS are measure of changes in pigmentation from baseline, such scores were not available at baseline. As such, baseline patient-level utility estimates were generated by applying baseline "prior therapy" TRuE-V sample VitiQoL scores to the following Begum et al. VitiQoL algorithm:

   $EQ\text{-}5D_{VitiQoL} = 0.9652 - 0.00205 * \text{Total VitiQoL Score}$

9. Next, the patient-level data utility data generated through steps 2 and 3 above were added to the TRuE-V dataset as if they were additional data fields, and regression analyses were performed to estimate the determinants of changes in patient utility from baseline to 24 weeks (and in a separate analysis not used in the company base case, of changes in patient utility from baseline to 52 weeks). The technical report embedded within Appendix O of the CS reported that a model of the following general form was applied to a stepwise selection procedure to determine final variable selection according to minimum Schwarz Bayesian Information criterion:

   $\text{Change from Baseline (CFB)} = \text{Baseline EQ-5D utility} + \text{Age} + \text{Sex} + \text{Skin Type (Fitzpatrick Scale)} + \text{Disease Status} + \text{Treatment} + \text{F-VASI 50 Response} + \text{F-VASI 75 Response} + \text{F-VASI 90 Response} + \text{Baseline EQ-5D} * \text{Treatment Interaction}$

   After final model selection, the technical report stated that predictions of CFB utility were derived through least squares means (marginal means) analysis on the final models after variable selection.

From this process, applied to the "prior therapy" TRuE-V sample, the company derived most of the estimates presented as the utility data informing the company analysis in Table 37 of the

CS, reproduced as Table 20, below. That is, the "No response", "F-VASI50-74", "F-VASI75-89" and "F-VASI90" estimates in Table 20 were generated through this process†.

Table 20: Reproduction of CS Table 37 – combined results informing the company's base case utility assumptions

State	Utility value: mean (standard error)	95% CI (Lower, Upper)	Justification
Baseline	0.879 (0.003)	0.874, 0.884	VitiQoL baseline utilised as F-VASI mapping produced no available baseline data [36]
No response	-0.082*	-0.087, -0.077	F-VASI (DP: -37.5%) was the best performing measure in the mapping algorithm [36]
F-VASI50-74	0.010*	-0.007, 0.028	
F-VASI75-89	0.056*	0.037, 0.074	
F-VASI90	0.066*	0.047, 0.084	

Abbreviations: F-VASI, facial vitiligo area scoring index; 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; VitiQoL, vitiligo-specific quality-of-life instrument
Source: Information presented in Section B.3.4.3.3 of the company's submission. Source data from Incyte, technical report for statistical analysis and utility modelling [Data on file] [36]

The data in Table 20 warrant careful interpretation that is lacking in the CS. First, the data presented under the column headed "Utility value: mean (standard error)" are not a collection of mean utility values as implied by the heading of the Table's second column. Instead, they are a baseline utility value and a collection of decrements applied separately to said utility value to generate health state utility values for the company's model. Table 21 summarises the expected utility values implied by the estimates in Table 20 and applied as health state utility values in the company's base case deterministic analysis. However, the outcome descriptions in the first column of Table 20 and Table 21 are different to the company's health state descriptions, as presented in the model schematic in Figure 5. Table 22 summarises the utility values associated with each model health state in the company's deterministic base case analysis.

† Note: The EAG highlights that the technical report embedded within Appendix O of the CS did not contain the results the EAG provides in Table 20.

Table 21: Absolute expected utility values implied by Table 18 and applied in the company's model

Description	Utility value assumed in company's deterministic analysis
Baseline	0.879
No response	0.797
F-VASI50-74	0.890
F-VASI75-89	0.935
F-VASI90	0.945

Table 22: Health state utility values applied in the company's deterministic analysis

Health state	Utility value assumed in company's deterministic analysis
Initial period	0.879
Maintenance period	0.935-0.945, dependent on response level
Stable	0.945
Retreated	0.879
Stable retreated	0.945
Non-response	0.797

There are clear issues with the company's approach to estimating and applying health state utility assumptions. Perhaps the most notable are listed as follows.

1. The number and strength of assumptions required to go from TRuE-V F-VASI data to the the utility values in Table 22, as set out in this section so far, called into question the reliability of the utility values as evidence-based estimates for decision making.
2. The quality of reporting by the company with respect to the approach and justification for each choice and assumption required to reach the utility values in Table 22 was a barrier to review and further reduced confidence in the appropriateness of the values selected.
3. As illustrated by EAG clarification question B15, the expected utility values assumed for "Maintenance period", "Stable" and "Stable retreated" health states were higher than the age-equivalent general population utility value from a source commonly cited in NICE appraisals[37]. Notably, this same source was used in the company's own model to adjust utility for the effect of ageing over the model's time horizon.

4. Importantly, all estimates other than that for the “Initial period” in Table 22 (“Baseline” in Table 21) were based on analysis of changes from baseline, where the baseline estimate was derived from a different measure and algorithm than all post-baseline data. Any interpretation of these values warrants extreme caution. When such values are in excess of general population estimates, there is clear reason to doubt their plausibility.
5. The company’s own approach estimated a utility value of 0.890 for patients achieving F-VASI50-74 at 24 weeks, as documented in Table 21. Yet, in the company’s model, patients achieving F-VASI50-74 are categorised as “Non-responders” and assigned a utility value of 0.797.
6. As noted in Section 3, the company’s clinical evidence submission did not demonstrate a treatment effect upon patient HRQoL, nor on important domains of HRQoL expected to be affected by ruxolitinib, such as anxiety and depression. The EAG was concerned that this evidence had been selectively set aside in preference of an approach that estimated a utility benefit from an F-VASI benefit.
7. As also noted in Section 3, the company’s evidence submission was clear in noting the humanistic burden of vitiligo. For example, the company cited that 54.2% of patients in the VALIANT study reported symptoms of moderate-to-severe depression in B.1.3.1.3 of the CS. Meaningful accounts of disease burden were also provided in Patient Body and Professional Organisation submissions from Vitiligo Support UK and the British Association of Dermatologists, respectively. The EAG was concerned that the company’s utility values may lack face validity in this context, in comprising a baseline utility value similar to an age-equivalent general population estimate and response-defined utility values that exceed this general population estimate.

For these reasons, the EAG noted the company’s approach to capture patient HRQoL effects in the cost-effectiveness analysis as a Key Issue (Key Issue 6). The importance of uncertainty around the company’s utility assumptions for cost-effectiveness results is explored in Section 6 of this report.

On top of the issues with the approach to capture health state utility values discussed above, the company’s economic analysis did not in any way account for the HRQoL implications of adverse events, despite treatment-emergent adverse events affecting 47.7% of ruxolitinib patients in the pooled TRuE-V population, as documented in Table 23 of the CS. In EAG clarification question B16, the EAG asked the company to incorporate into its analysis utility

implications for the adverse event data in Table 24 of the Document B of the company submission (treatment-emergent adverse events occurring in ≥ 1% of patients in any treatment group). In response, the company declined to do so, without reasonable justification. In the context of the potential magnitude of QALY gains for ruxolitinib, the EAG considered that it was plausible that accounting for the HRQoL implications of adverse events appropriately could meaningfully affect cost-effectiveness results. Accordingly, and as documented in Section 1.5, the absence of expected utility implications of adverse events from the company's analysis is, alongside issues with the company's approach to account for cost implications of such adverse events (documented in Section 4.2.9), EAG Key Issue 7.

4.2.9. Resources and costs

The company report identifying 11 publications reporting healthcare resource and cost data for people with vitiligo in their SLR of economic literature, but do not report if, how or for what reason any of these 11 studies were used to inform their cost assumptions. The company's cost assumptions broadly fell under three categories, defined here as: treatment acquisition and administration; disease management; and adverse event management. The company's approach to assume costs for each of these categories is documented and critiqued in this section in turn.

Issues with the company's approach to treatment acquisition and administration and disease management costs, documented across sections 4.2.9.1 and 4.2.9.2, led the EAG to conclude that the cost assumptions in the company's analysis biased cost-effectiveness results in favour of ruxolitinib. Together, these issues comprised EAG Key Issue 5. Issues with the company's approach to capture adverse event costs, documented in section 4.2.9.3, along with the absence of HRQoL implications of adverse events critiqued in section 4.2.8, together comprise EAG Key Issue 7.

4.2.9.1. Treatment acquisition and administration

The price of ruxolitinib was £[redacted] per 100g tube in the company's analysis. The company described this price as a list price [redacted]. The company assumed that the combined acquisition, dispensation and administration cost of ruxolitinib was equal to £[redacted] per 100g tube, at list price. That is, the company assumed that there was no dispensation or administration cost associated with ruxolitinib, which underestimated costs on the intervention arm of the analysis, particularly if ruxolitinib was considered as a potential end-of-line treatment, which the EAG considered to be a possibility. In

the CS, the company reported submitting a Patient Access Scheme (PAS) including a simple [redacted]% discount to the acquisition price of ruxolitinib. The company's cost-effectiveness results assumed that this PAS discount would hold in practice.

The PAS-adjusted ruxolitinib acquisition price combined with dosing and time-on-treatment assumptions comprised total ruxolitinib treatment costs in the company's analysis. Adjusted for PAS discount and the company's dosing expectations, the per 4-week cycle ruxolitinib acquisition cost in the company's analysis was £[redacted]. The company's approach to model ruxolitinib dosing was EAG Key Issue 4, as set out in Section 4.2.4, while the EAG also held concerns about the model's deviation from observed time-on-treatment in the TRuE-V study programme, as discussed in Section 4.2.7.

On the comparator arm of the company's analysis, the acquisition cost of vehicle cream was assumed to be equal to the per ml cost of suncream, using a British National formulary (BNF) estimate of £9.70 per 125ml bottle. Vehicle cream dosing was assumed to be equal to ruxolitinib dosing using pooled TRuE-V data, as described in in Section 4.2.4, assuming 1ml vehicle cream equals 1g vehicle cream. Adjusted for the company's dosing expectations, the per cycle vehicle cream acquisition cost in the company's analysis was £[redacted]. Vehicle cream time-on-treatment assumptions were based on TRuE-V vehicle cream time-on-treatment data in a similar manner to the ruxolitinib arm, as described in Section 4.2.7.

Concomitant treatments were assumed for all alive model states except for "Stable" states, where no treatment costs were assumed. For "initial", "maintenance" and "retreated" states, these costs were assumed equivalent across arms and totalled £17.66 per 4-week model cycle. Concomitant treatments were assumed to comprise suncream, vitamin D supplement, camouflage cream and fixing powder. The EAG noted that the company was therefore effectively applying a cost of suncream twice in the vehicle cream arm of the analysis. In addition, the EAG noted that in practice, ruxolitinib use would limit a person's freedom to apply suncream when wanted, as discussed in Section 3.2.2. The company did not account for this in their analysis.

Importantly, as well as intervention and comparator treatment costs, the company separately defined "BSC" treatment costs, which they assumed for the "non-response" state of each arm of the model. As patients on the vehicle cream arm of the analysis spent longer incurring costs in the "non-response" state over the model's time horizon, overestimating costs for this state would bias the analysis in favour of ruxolitinib. BSC treatment costs were assumed to comprise £19.05

of concomitant treatment costs (assuming different levels of concomitant treatment use than in "initial", "maintenance" and "retreated" states) and, as noted in Section 4.2.5, £643.24 of hospital-based NB-UVB costs, every 4-week cycle.

The EAG had several notable issues with the NB-UVB assumptions applied in the "non response" health state of the model:

1. The company assumed that [redacted]% of those in the "non-response" state received NB-UVB, based on a simple average of the proportion of UK patients who had ever used light, laser or NB-UVB therapy and the proportion of UK healthcare professionals who recommended such therapy in the Vitiligo and Life Impact Among International Communities (VALIANT) study; a global survey study exploring the natural history and management of vitiligo from patient and healthcare professionals[38]. In the EAG's view, such a source and consideration of an active, effective treatment assumption was inappropriate for a health state that was characterised as a "non-response" state. As noted in Section 4.2.5, clinical advice to the EAG suggested that in practice, patients in long-term non-response were likely to become disengaged with the healthcare system, with unmet need and low healthcare costs.
2. The company assigned a cost of £140.84 to every NB-UVB session, based on the 2021/22 NHS Reference Cost of an outpatient dermatology procedure. Assuming three sessions per week over nine months, the company assumed that this cost was incurred 117 times per course of NB-UVB; a total cost of £16,478.36. Yet, clinical advice received by the company, provided to the EAG in response to EAG priority clarification question B4, informed the company that for facial vitiligo, a home-based approach would be suggested, with handheld device training being provided in the hospital and use monitored every 3-4 months unless issues arose. This advice appeared to be in line with practice in the UK NHS-based HI-Light trial. A 2021 economic evaluation of topical corticosteroid and home-based NB-UVB based on HI-Light trial results used similar assumptions, and estimated a total NHS cost of a course of NB-UVB of £775[39]. Clinical advice to the EAG noted that hand-held NB-UVB devices were not available at every NHS centre; the average NHS cost of a course of NB-UVB may be greater than £775 as a result, but the EAG expected that £16,478.36 was a marked overestimation. Further, the NHS resource burden implicit in the company's costing assumptions would surely reduce the proportion of patients expected to be able to access NB-UVB treatment.

3. The company assumed that an equivalent of a nine-month course of hospital-based NB-UVB occurred every year, for those [redacted]% of patients in the "non-response" state assumed to receive NB-UVB. The £643.24 per cycle cost was calculated as [redacted]% * £140.84 * 177 sessions * (28 days / 365.25 days), and was assumed to apply to the "non-response" state every cycle, for as long as treatment costs were assumed plausible in this state – until 10 years from baseline in the company's analysis, as critiqued in Section 4.2.5. From the EAG's understanding of capacity constraints in NHS Dermatology departments, near continuous NB-UVB was not plausible for any vitiligo patient, let alone on average. The EAG's clinical advisor explained that there was no limit on the number of NB-UVB courses a patient could receive, but the decision to recommend a second course would be based on response to NB-UVB previously; even if retreatment with NB-UVB was recommended, there may be a one-year wait between NB-UVB courses. Further, there was a tendency within the NHS to prioritise NB-UVB capacity for patients with conditions that respond to NB-UVB more quickly than vitiligo.

With respect to EAG concerns over the company's proposed positioning of ruxolitinib (Key Issue 1), the EAG considered that a comparison to vehicle cream was only potentially appropriate as an end-of-line comparison. In this instance, assuming any NB-UVB use after ruxolitinib or standard of care treatment would be inappropriate. However, even if the company's positioning of NB-UVB after ruxolitinib treatment could be considered appropriate, the EAG identified clear issues with the company's characterisation of NB-UVB in the NHS setting. Overall, the company's approach to cost for NB-UVB treatment overestimated the expected cost in several ways, biasing cost-effectiveness results in favour of ruxolitinib.

4.2.9.2. Disease management

The company's analysis assumed that disease management costs were incurred every cycle, in each of the alive health states of the model. The categories of disease management resource that the company considered were: Dermatologist outpatient consultation; Dermatologist telephone consultation; Dermatologist nurse visit; GP consultation; Accident & Emergency (A&E) Visit; Psychological support. The company assumed that the amount of these resources used differed across (i) "Initial", "Maintenance" and "Retreated" states, (ii) "Stable" states and (iii) the "non-response" state. Generally, "Stable" states were assumed to use less disease management resource than "Initial", "Maintenance" and "Retreated" states, while the "non-response" state was associated with the highest resource use burden, as documented in Table 41 of the CS. The company reported that their resource use assumptions were based on a

combination of the 2021 Sachs et al. economic evaluation of HI-Light trial outcomes,[39] referenced in Section 4.2.9.1, and clinical expert opinion.

The company's disease management resource use assumptions implied engagement with the health service at least every 2 months, across alive health state, and produced the following 4-weekly disease management cost estimates:

- "Initial", "Maintenance" and "Retreated" states: £308.31
- "Stable" states: £132.37
- "Non-response" state: £548.22

The EAG was concerned that the company's approach overestimated disease management costs, in a manner that biased cost-effectiveness results in favour of ruxolitinib. Clinical advice to the EAG suggested that the company's psychological support assumptions were inaccurate. The EAG's clinical adviser noted that many clinicians did not screen for psychological distress; their expectation is that only around 15% of patients were directed towards psychological support resources. Even if this happens, the direction would be towards self-referral for NHS Talking Therapies (formerly IAPT: Improving Access to Psychological Therapies)[40] for those with moderate or severe distress and to self-help resources for those with mild distress. The EAG's clinical adviser's understanding was that waiting lists for such services meant that some self-referred patients disengage, while others may seek private pyschological support instead.

The EAG was also concerned with the assumption of ongoing Dermatologist appointments in the "non-response" state. As noted in Section 4.2.9.1 and elsewhere in this document, if a comparison to vehicle cream was only potentially appropriate for end-of-line positioning, no NHS Dermatology appointments would be expected in this "non-response" state. Even taking the company's proposed positioning, a per patient expectation of ongoing engagment with NHS Dermatologists around every 2 months for 10 years post baseline does not tally with the EAG's understanding of resource constraints in Dermatology departments and the impact of this on typical uptake.

Further, the EAG noted that the Dermatologist and GP appointment frequency assumptions for the "non-response state" were estimates from the NB-UVB + TCS arm of Sach et al[39]. As such, in the company's base case, the "non-response" health state costs included (i) NB-UVB treatment costs that were calculated based on the cost of Dermatology appointments, as

described in Section 4.2.9.1 and (ii) separately, Dermatology appointment costs to capture disease management resource use. This was clearly double counting.

Overall, for reasons documented here, the EAG was concerned that the company's analysis overestimated disease management costs in a manner that biased cost effectiveness results in favour of ruxolitinib.

4.2.9.3. Adverse event management

The company's analysis captured treatment-arm specific expectations for adverse event costs, using incidence rates of adverse events occurring in ≥4% of patients in either arm up to week 24 across TRuE-V1 and TRuE-V2, as reported across B.3.3.5 and B.3.5.3 of the CS (Doc B). This accounted for incidences of application site acne, application site pruritis, nasopharingitis, headache and upper respiratory tract infection; though the incidence of the latter appeared to have been <4% across arms, from Section B.3.3.5. The company's approach produced expected per cycle adverse event costs of £4.11 and £1.67, for ruxolitinib and vehicle cream arms of the company's analysis, respectively.

In EAG clarification question B16, the EAG asked the company to extend the scope of adverse events included in the cost calculation, to capture treatment-emergent adverse events occurring in ≥ 1% of patients in any treatment group. In reply, the company declined to amend their original approach. Although the technology under appraisal was a topical treatment and there were no clear safety concerns in the TRuE-V studies, the EAG asked for this, alongside consideration of the HRQoL consequences of such events, for several reasons. Firstly, 4% is an arbitrary and high cut-off, while 1% is an established cut-off for "common" adverse events, as noted in European Medicines Agency documentation[41]. Secondly, if this appraisal led to a positive recommendation for ruxolitinib at the end of the existing treatment line, it will replace no treatment, and thus definitively introduce toxicity. Thirdly, the dosing data received in response to EAG clarification questions and documented later in Section 6.2.3 suggested that some patients in the TRuE-V trials exposed themselves to more ruxolitinib than recommended, which may have resulted in safety issues unanticipated with intended use.

5. COST-EFFECTIVENESS RESULTS

5.1. Company's cost-effectiveness results

The company results presented throughout section 5 reflect the proposed PAS-adjusted price of ruxolitinib, as reported in section 4.2.9.1.

5.1.1. Base case results

The company's post-clarification questions deterministic and mean probabilistic base case cost-effectiveness results are summarised in Table 23. The deterministic analysis underestimated total QALYs and overestimated total costs across model arms, relative to the mean probabilistic analysis. The company's mean probabilistic results were produced using 2,000 probabilistic model iterations, with evidence of testing for robustness of summary results to additional iterations up to 2,000 iterations presented.

The EAG placed little weight on the company's summary base case results, owing to the various issues in the company's analysis documented through sections 0, 2 and 4. As documented in Sections 2 and 4 and comprising Key Issue 1, in the EAG's view the company's analysis did not address the decision problem, as defined by the company for a subgroup of the final scope. As a result, the analysis results were fundamentally of little value to the appraisal. Further issues identified throughout Section 4 together suggested bias in the company's analysis in favour of ruxolitinib.

Table 23: Company base case results

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Company deterministic base case					
Vehicle cream	[redacted]	[redacted]	-	-	-
Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	£13,634
Company mean probabilistic base case					
Vehicle cream	[redacted]	[redacted]	-	-	-
Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	£14,676

Abbreviations: QALYs, quality adjusted life years

5.2. Company's sensitivity analyses

Though the EAG placed little weight on the company's headline cost-effectiveness results, the company's sensitivity analyses had merit in characterising some of the parameter uncertainty around the company's results, and in illustrating some important areas of sensitivity in the company's analysis.

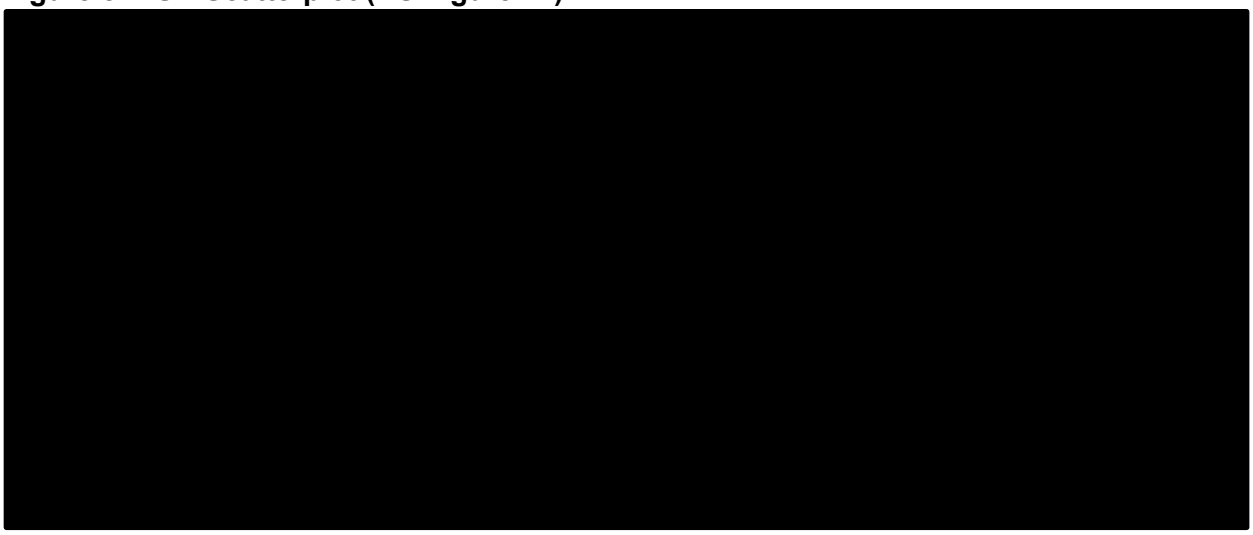
5.2.1. One-way sensitivity analysis

The company's one-way sensitivity analysis (OWSA) used a mixture of distributional assumptions across parameters, as partially reported in section B.3.6.2 of the CS. Section B.3.8.2 of the CS reported OWSA results as a tornado diagram showing the 20 parameters that led to the greatest variation in ICER results. Limitations in the parameter testing descriptions in this diagram meant that its reproduction in this report would be of little value. In short, base case deterministic company cost-effectiveness results were most sensitive to uncertainty around response rate estimates, discontinuation rate estimates and NB-UVB assumptions in the "non-response" state. In the extreme, the company's OWSA caused ICER estimates to vary from around £1,000 to over £30,000 per QALY gained.

5.2.2. Probabilistic sensitivity analysis

Figure 8, below, reproduces the probabilistic sensitivity analysis (PSA) scatterplot presented as Figure 22 in the CS. The distribution of PSA iteration results gave a picture of the parameter uncertainty around the mean PSA results in Table 23, above. The probability that ruxolitinib was cost-effective at a willingness-to-pay threshold of £20,000 per QALY gained in the company's probabilistic analysis was [redacted]%.

Figure 8: PSA Scatterplot (CS Figure 22)



5.2.3. Scenario analyses

The company presented results from seven scenario analyses. Descriptions of each of these scenarios, as reported by the company, are provided in Table 24. Scenario analysis results as reported by the company are shown in Table 25. Despite only comprising seven scenarios, the company's scenario analysis highlighted some important model sensitivity. Perhaps most notably, using the published mapping algorithm for the Vitiligo Noticeability Scale in place of the F-VASI algorithm from the same study (as described in section 4.2.8) caused the estimated QALY gain associated with ruxolitinib to diminish to [redacted] with a resultant ICER of £398,929. Another notable scenario illustrated the sensitivity of company-preferred results to when costs in the "non-response" state were no longer asumed to be incurred. When this parameter was set to 5 years from baseline rather than 10 years from baseline, the estimated incremental cost of ruxolitinib more than doubled and the estimated ICER increased to £39,272.

Two of the company's seven scenarios were analyses for different patient populations: (i) the overall TRuE-V population and (ii) the TRuE-V subgroup with Fitzpatrick skin type IV-VI. Using response and treatment discontinuation rates estimated from these samples and otherwise keeping all model settings constant, the company's analysis predicted that ruxolitinib was less cost-effective in the overall population than in the "prior therapy" population and highly cost effective (dominant) in the Fitzpatrick skin type IV-VI population.

Table 24: Overview of company's scenario analyses (CS Table 46)

No	Model scenario	Base Case	Description/Justification
1	Utility data source: F-VASI (DP: -25%)	Utility data source: F-VASI (DP: -37.5%)	This scenario explored the impact of utilising alternative bandings in the F-VASI mapping algorithm. Depigmentation categorisation I: Percentage change of -25% (i.e., all patients with depigmentation were truncated to having skin pigmentation loss not greater than 25%) [DP: -25%] (Section 4.2.8)
2	Utility data source: VNS	Utility data source: F-VASI (DP: -37.5%)	VNS was the secondary endpoint in the TRuE-V studies [32]. As such, mapping from this endpoint was considered for scenario analyses.
3	Model time horizon: 10 years	Model time horizon: Lifetime (63 years)	This scenario explores the impact of a shorter time horizon in the model.
4	Stop costs in the non-response state: 5 years	Stop costs in the non-response state: 10 years	This scenario explores the impact of varying the length of time costs are incurred in the non-response state. This aligns with clinical feedback where clinicians noted that patients experience treatment fatigue and patient choice varies over time [5].
5	Stop costs in the non-response state: Lifetime	Stop costs in the non-response state: 10 years	This scenario explores the impact of varying the length of time costs are incurred in the non-response state. This aligns with clinical feedback where clinicians noted that patients experience treatment fatigue and patient choice varies over time [5].
6	Overall population	Prior therapy sub-group	This scenario explores the impact of assessing the overall population recruited in the TRuE-V studies.
7	Patients from overall population with Fitzpatrick skin type IV-VI	Prior therapy sub-group	The Fitzpatrick IV-VI categorisation was chosen as darker skin types are associated with a greater patient burden [42] including use of a significantly greater number of treatments [43]. This categorisation has been used in a recent study which assessed the importance of facial involvement for patients [44].

Abbreviations: DP, depigmentation; F-VASI, facial vitiligo area scoring index; VNS, vitiligo noticeability scale

Table 25: Summary of key cost-effectiveness results from scenario analyses (CS Table 47)

No	Model scenario	Treatment	Total costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER vs vehicle cream
1	Utility data source: F-VASI (DP: -25%)	Vehicle cream	[redacted]	[redacted]	-	-	-
		Ruxolitinib cream	[redacted]	[redacted]	[redacted]	[redacted]	£20,348
2		Vehicle cream	[redacted]	[redacted]	-	-	-

No	Model scenario	Treatment	Total costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER vs vehicle cream
	Utility data source: VNS	Ruxolitinib cream	[redacted]	[redacted]	[redacted]	[redacted]	£398,929
3	Model time horizon: 10 years	Vehicle cream	[redacted]	[redacted]	-	-	-
		Ruxolitinib cream	[redacted]	[redacted]	[redacted]	[redacted]	£5,687
4	Costs in the non-response state stop at: 5 years	Vehicle cream	[redacted]	[redacted]			
		Ruxolitinib cream	[redacted]	[redacted]	[redacted]	[redacted]	£39,272
5	Costs in the non-response state stop at: Lifetime	Vehicle cream	[redacted]	[redacted]	-	-	-
		Ruxolitinib cream	[redacted]	[redacted]	[redacted]	[redacted]	£3,894
6	Population: Overall	Vehicle cream	[redacted]	[redacted]	-	-	-
		Ruxolitinib cream	[redacted]	[redacted]	[redacted]	[redacted]	£19,179
7	Population: Fitzpatrick skin type IV-VI	Vehicle cream	[redacted]	[redacted]	-	-	-
		Ruxolitinib cream	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: DP, depigmentation; F-VASI, facial vitiligo area scoring index; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

5.3. Model validation and face validity check

In B.3.11 of the CS, the company reported conducting validation exercises with “clinicians and health economists” throughout model conceptualisation, development and finalisation, though no evidence of such validation or what it comprised was provided in the CS. In response to priority EAG question B4, the company provided documentation from meetings with three anonymised “Clinical Expert”s and one anonymised “Health Economist”. Each expert was interviewed separately, in the presence of at least six attendees from the company and their consultancy. Two of the clinical experts were interviewed once, one was reinterviewed; these interviews each lasted 90-120 minutes and were conducted between January 2022 and June 2023. The health economist was interviewed three times between March 2022 and May 2023, in meetings lasting 60-120 minutes. The company appeared to have selectively used advice from these meetings. For example, the questions put to the clinical experts on response definitions and answers received across each clinical expert acknowledged the clinical relevance of VASI50 at 24 weeks. Yet, the company’s model categorised those achieving an “initial response” of VASI50-74 as non-reponders.

There was no evidence that the company validated model outcomes against published estimates from external studies or with clinical experts.

The company reported conducting a full quality control assessment following finalisation of the model, and provided as evidence the documentation produced by an internal quality control checklist exercise within Appendix N of the CS. Despite this being described as a full quality control, only some of the relevant checks in the document embedded in Appendix N appeared to have been conducted. The submitted model passed standard internal consistency and stress checks performed by the EAG as reported in section 4.2.2. However, sheet-by-sheet EAG review of the company model revealed clear issues with logic applied in the analysis, documented in section 4.2.5 and comprising part of Key Issue 3.

6. EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

The EAG identified limitations within the company's base case and explored the impact of parameter values, and assumptions, which the EAG believed were more plausible.

This section is organised as follows: Section 6.1 details the impact of errors identified in the EAG's validation of the executable model. Section 6.2 details a series of scenario analyses exploring the robustness of the cost-effectiveness results to specific assumptions and additional uncertainties identified by the EAG. These analyses were conducted within the company corrected base-case analysis (presented in Section 6.1). The scenario analyses presented in Section 6.2 focus on exploring the following issues and uncertainties:

- Alignment of management costs with clinical practice (Key Issue 1 and Key Issue 5)
- Face validity of utility values (Key Issue 6)
- Dosing of ruxolitinib (Key Issue 4)
- Duration of costs application in 'no response' (Key Issue 5)
- Approach to handling missing data for clinical data (Key Issue 3)
- Retreatment with ruxolitinib (Key Issue 3)

As this list indicates, neither the EAG's scenario analyses nor the EAG-preferred analyses addressed every Key Issue identified throughout Sections 2, 3 and 4. Specifically, EAG amendments have not been able to address important elements of Key Issue 1 (The clinical and cost effectiveness of ruxolitinib as compared to established treatment options is unknown), Key Issue 2 (The clinical effectiveness evidence presented by the company was not representative of the target population and the population used in the company's economic evaluation), Key Issue 3 (Cost-effectiveness model's structural assumptions and use of clinical effectiveness data) and Key Issue 7 (Approach to adverse event assumptions in the cost-effectiveness model). As such, the EAG only presents *tentative* preferred analyses in this report.

In Section 6.3, the EAG's tentative preferred base-case results are based on a combination of the analyses presented in Section 6.2. Finally, Section 6.3 presents conclusions of the cost-effectiveness section of the EAG's report.

6.1. EAG corrections and adjustments to the company's base case model

The EAG corrections have addressed four errors in the company's model:

- The "initial period" of the model was intended to capture 6 cycles (i.e., 24 weeks), but instead captured 7 cycles (i.e., 28 weeks) – see Section 4.2.5. The EAG corrected this to limit the initial period to 6 cycles only. At factual accuracy check stage of the appraisal, the company highlighted that the same 'fix' should be applied for the long-term part of the model, and so the relevant cell values were reduced by 4 weeks (i.e., 1 cycle) accordingly.
- In response to clarification question B11, the company confirmed that since it populated its model, the BNF was updated which led to some costs no longer aligning with the stated sources – see Section 4.2.9. The EAG therefore amended these costs by updating cost sources to reflect current BNF costs using company's provided appendix, following cross-checking with the NHS eMIT for generic medicine costs (which were used in preference to the BNF if lower).
- The company's model included a calculation error where patients were mistakenly omitted from the numerator of a proportion calculation – see Section 4.2.7. The EAG corrected this.
- In Appendix M of the CS, the company provided variance-covariance matrices for utility regression analyses informing the company's health state utility assumptions. However, these were not integrated within the company's model to appropriately inform the probabilistic analysis. The EAG included the variance-covariance matrix, with implications for the probabilistic analysis.

The fixes are labelled as 'EAG_fix_1' to 'EAG_fix_4', and 'EAG_FAC_2', within the EAG-adapted model. When combined, these corrections collectively lead to a small reduction in the company's base-case deterministic ICER (£13,634 versus £13,031) and the mean probabilistic ICER (£14,676 versus £14,257), when the probabilistic analysis was based on 2,000 PSA iterations as in the company base case.

Table 26: EAG-corrected company base case results

	Discounted costs (£)	Discounted QALYs	Δ discounted costs (£)	Δ discounted QALYs	ICER (£/QALY)
EAG-corrected company deterministic base case					
Vehicle cream	[redacted]	[redacted]			

	Discounted costs (£)	Discounted QALYs	Δ discounted costs (£)	Δ discounted QALYs	ICER (£/QALY)
Ruxolitinib cream	[redacted]	[redacted]	[redacted]	[redacted]	13,031
EAG-corrected company mean probabilistic base case					
Vehicle cream	[redacted]	[redacted]			
Ruxolitinib cream	[redacted]	[redacted]	[redacted]	[redacted]	14,257

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years.

6.2. Exploratory and sensitivity analyses undertaken by the EAG

Several exploratory analyses were undertaken to investigate the impact of alternative settings and assumptions on the cost-effectiveness results.

6.2.1. Alignment of management costs with clinical practice

As discussed in Sections 4.2.4 and 4.2.5, and central to Key Issue 1, the company's model may be considered to better reflect the potential use of ruxolitinib *following* second-line treatment options, rather than *between* first- and second-line options as the company proposed. This is because it does not provide a comparison to second-line treatment options, and instead presents a comparison to vehicle cream which is not a comparator relevant to this appraisal in this setting. In addition, based on clinical advice provided to the EAG, some of the cost assumptions informing the model were considered unlikely to reflect current NHS practice. For these reasons, the EAG considered the impact on results if resource use and cost assumptions model was edited to align with the use of ruxolitinib in an end-of-line setting (where vehicle cream could be considered as a proxy for 'no treatment', which may be considered a relevant comparator in this setting) and current NHS practice, which involved:

- Setting the cost of vehicle cream to £0 (since vehicle cream is not a treatment used in practice, and sun protection is already accounted for as part of concomitant therapy)
- Removing the cost of NB-UVB from the 'no-response' health state (given that this would be offered to patients in a second-line setting)
- Reducing the proportion of patients receiving psychological support to 15% (based on clinical advice provided to the EAG)

These changes were combined into one analysis, labelled 'EAG_1' in the model.

6.2.2. Face validity of utility values

The company's approach to estimating utility values, as described in Section 4.2.8, was both complex and subject to substantial limitations, which together contributed to Key Issue 6. As described within Section 4.2.8, the EAG had several key concerns with the company's base-case utility values. Two such concerns were investigated in EAG exploratory analyses:

- As illustrated by EAG clarification question B15, the expected utility values assumed for "Maintenance period", "Stable" and "Stable retreated" health states were higher than the age-equivalent general population utility value from a source commonly cited in NICE appraisals[37]. Notably, this same source was used in the company's own model to adjust utility for the effect of ageing over the model's time horizon.

- The company's central approach to utility value estimation produced a utility value of 0.890 for patients achieving F-VASI50-74 at 24 weeks, as documented in Table 21. Yet, in the company's model, patients achieving F-VASI50-74 are categorised as "Non-responders" and assigned a utility value of 0.797.

To address these issues, the EAG conducted the following two exploratory analyses:

1. capped all utility values using general population estimates and limited the reduction in utility from baseline to no response to 5% (i.e., the utility for the 'no response' health state was assumed to be 95% of the utility value for baseline).
2. capped all utility values using general population estimates and applied a weighted average of the utility value estimated for patients with F-VASI50-74 and 'no response' to the "non-response" state, using the proportion of patients in the ruxolitinib arm in each category measured at 24 weeks. Please note: at the factual accuracy check stage of the appraisal, the company highlighted that that EAG's analysis included a numerical error in determining the relevant weights, which was subsequently corrected.

These changes were included within the model, labelled 'EAG_2' and 'EAG_FAC_1' in the model, alongside a multi-way sensitivity analysis to consider alternative combinations of utility values.

6.2.3. Ruxolitinib dosing

The average dose of ruxolitinib used by people with vitiligo in practice was challenging to estimate for a variety of reasons, as discussed in Section 4.2.4. These included (but may not be limited to): differences in extent of depigmentation, body surface area, patient preference for treating specific regions, adherence to treatment, and interpretation of dosing instructions. In the company's base-case analysis, the median dose across both treatment arms across the double-blind period of the TRuE-V studies was assumed to represent expected ruxolitinib use. This gave an average daily dose of 4.03g, which was equivalent to 1.13 tubes per 28 days. As described in Section 4.2.4 and comprising Key Issue 4, the EAG was concerned that the company's dosing assumptions may substantially underestimate ruxolitinib use, in a manner that biased cost-effectiveness results notably.

The EAG would generally prefer to use the mean dose for patients only receiving ruxolitinib (i.e., excluding dosing data for the vehicle cream arm) across both the TRuE-V studies. The mean dose for this sample, as reported by the company in response to clarification question B10, was 7.61g daily; equivalent to 2.13 tubes per 28 days. Given that the SmPC for ruxolitinib advised that no more than two tubes should be used per patient per month, an alternative estimate of the average (and maximum) daily dose would be 6.57g, which was equivalent to exactly two tubes per 30.4375 days. Consequently, in two alternative analyses, the EAG applied either a daily dose of 6.57g or the mean daily dose of 7.61g, acknowledging that the latter exceeds the advised upper limit of two tubes per month, but nevertheless represented the observed average use of ruxolitinib in the TRuE-V studies. Furthermore, the EAG noted that the average dose of ruxolitinib appeared to increase in the TRuE-V LTE study (see company's response to clarification question B10).

Finally, the EAG also considered a scenario analysis in which two tubes are provided to patients every 28 days, in keeping with 28-day prescribing patterns, the model cycle length, and the guidance given to patients as part of the TRuE-V studies (i.e., 60g per 7 days). This scenario was introduced following a correction made to the interpretation of "two tubes per month" at the factual accuracy check stage of the appraisal.

Alternative dosing assumptions were incorporated into the model, labelled as 'EAG_3' and 'EAG_FAC_3'.

6.2.4. Duration of costs application in 'non-response'

The company's model assumed that all costs in the 'non-response' state would cease from 10 years following model entry, without clear and complete rationale. It was the EAG's view that 'time to no further costs' would be linked with residence in and time since arrival to the 'non response' state, as opposed to how much time has elapsed since model entry. Therefore, while the EAG acknowledged that some people may, in time, become disengaged with secondary care, the company did not substantiate its assumption with respect to the application of 10 years from model entry.

In a scenario analysis, the EAG removed the 10-year cap on accrual of costs in the 'no response' health state. This is labelled as 'EAG_4' in the model. In an alternative analysis, the EAG also considered applying 10 years' worth of costs for the proportion of patients that were no longer in a response or treated health state compared with the previous model cycle. This is labelled as 'EAG_sc_2' in the model.

The EAG presents these pragmatic exploratory analyses in lieu of a better alternative, as it would take a substantial amount of modelling work to specify tunnel states to track time since entry to the 'no response' health state, which would not be feasible within the timeframe of the EAG appraisal.

6.2.5. Approach to handling missing data for no regain of response

As noted in Section 4.2.7 and comprising part of Key Issue 3, the company's approach to handling missing data for the probability of not regaining response was erroneous. In addition, the EAG considered a more accurate estimate of this probability to be based on the assumption that missing data were likely to reflect non-response. Therefore, in a scenario conducted by the EAG (labelled 'EAG_5'), an alternative probability of not regaining response was used in place of the company's preferred 'average' approach.

6.2.6. Retreatment with ruxolitinib

The company's model structure assumed that patients who achieved F-VASI90 and became "Stable" but subsequently lost this level of repigmentation move to the 'Retreatment' health state (see Figure 5). At the clarification stage, the EAG asked the company to update its model to allow for an analysis in which retreatment for such patients was not assumed to be certain (clarification question B7). In response, the company included the ability for the proportion of

patients assumed to be re-treated to be varied between 0% and 100%, including a scenario using a value of 68% (though no citation was provided for this value).

Clinical advice to the EAG suggested that all patients would be offered re-treatment if they previously were deemed to respond sufficiently well to treatment following an initial course. However, as highlighted in Section 4.2.5 of this report, the expected continuation criteria used in NHS clinical practice may differ from the criteria used to determine transitions in the model structure. In addition, it remained unclear how many courses of treatment with ruxolitinib patients may undergo over their lifetime, and it was unclear if or how the effect of ruxolitinib may change if it was used in successive courses (especially accounting for patients starting treatment with likely differing extent of de-pigmentation compared with baseline). Consequently, the EAG noted that it was difficult to justify a preferred base-case setting for this parameter, within the constraints of the company's model.

In the absence of any clear rationale to deviate from the company's base-case setting of 100% retreatment (which in principle was supported by clinical advice to the EAG, notwithstanding the differences in continuation criteria as previously noted), the EAG adhered to the company's base-case assumption within its tentatively preferred base-case analysis. In sensitivity analysis, the EAG disabled re-treatment entirely to ascertain its impact on the cost-effectiveness results. This is labelled as 'EAG_sc_1' in the model.

6.2.7. Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

The EAG made the changes described in Sections 6.2.1 to 6.2.6 (labelled as 'EAG_1' to 'EAG_5', and 'EAG_sc_1' to 'EAG_sc_2' in the model). The results of these exploratory analyses (where each change has been made individually) are provided in Table 27.

Table 27: EAG's exploratory analyses with EAG fixes applied

Scenario	Section	Δ costs (£)	Δ QALYs	ICER (£/QALY)	+/- company base case
EAG-corrected deterministic company base case	6.1	[redacted]	[redacted]	13,031	-603
Alignment of management costs with clinical practice – removal of vehicle cream and NB-UVB costs, removal of dermatology visits for patients in 'no response' and	6.2.1	[redacted]	[redacted]	99,237	+85,603

Scenario	Section	Δ costs (£)	Δ QALYs	ICER (£/QALY)	+/- company base case
proportion of patients receiving psychological support set to 15% for all health states (EAG_1)					
Face validity of utility values – maximum utilities set to those of the general population and 'no response' utilities set to a weighted average of baseline and F-VASI50-74 values (EAG_2 and EAG_FAC_1)	6.2.2	[redacted]	[redacted]	21,640	+8,005
Face validity of utility values – maximum utilities set to those of the general population and 'no response' utilities set to an arbitrary reduction of 5% from baseline utility values (EAG_2)	6.2.2	[redacted]	[redacted]	25,822	+12,188
Ruxolitinib dosing – assume pooled mean dose for only the ruxolitinib arms of TRuE-V studies (EAG_3)	6.2.3	[redacted]	[redacted]	96,046	+82,412
Ruxolitinib dosing – assume a maximum recommended daily dose when two tubes per month (EAG_3)	6.2.3	[redacted]	[redacted]	71,894	+58,260
Ruxolitinib dosing – assume a maximum recommended daily dose when two tubes per 28 days (EAG_FAC_3)	6.2.3	[redacted]	[redacted]	85,146	+71,512
Duration of costs application in 'non-response' – set to lifetime (EAG_4)	6.2.4	[redacted]	[redacted]	3,567	-10,067
Duration of costs application in 'non-response' – alternative application based on lump sum (EAG_sc_2)	6.2.4	[redacted]	[redacted]	78,252	+64,618
Approach to handling missing data for no regain of response – assume non-response (EAG_5)	6.2.5	[redacted]	[redacted]	13,580	-54
Retreatment with ruxolitinib set to 0% (EAG_sc_1)	6.2.6	[redacted]	[redacted]	31,354	+17,720

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

6.3. EAG's preferred assumptions

As described in Section 6.2, the EAG presents two preferred analyses that differ only in their dosing assumptions, and considered all analyses "tentative", given the outstanding and unexplored uncertainty around Key Issues 1, 2, 3 and 7, collectively.

The following deviations from the EAG-corrected company base case applied to both EAG-preferred tentative base cases:

- Removal of vehicle cream and NB-UVB costs, removal of dermatology visits for patients in 'no response' and proportion of patients receiving psychological support set to 15% for all health states to align with clinical practice (Section 6.2.1; Key Issue 1 and Key Issue 5)
- Maximum utility values set to those of the general population, and 'no response' values set to a weighted average of baseline and F-VASI50-74 utility values (Section 6.2.2; Key Issue 6)
- Duration of costs applied for both drug acquisition and disease management set to lifetime (Section 6.2.4; Key Issue 3 and Key Issue 5)
- Missing data treated as non-response data in calculation of the probability of retreatment (given F-VASI<75 at week 52 leads to F-VASI<90 at week 104; Section 6.2.5; Key Issue 3)

EAG preferred, tentative base cases 1 and 2 differ with respect to expected ruxolitinib use assumptions only. Tentative Base Case 1 results, shown across Table 28 and Table 29, assume that ruxolitinib use in practice will reflect the pooled mean dose for the ruxolitinib arms of TRuE-V studies (7.61g). Tentative Base Case 2 results, shown across Table 30 and Table 31, assume ruxolitinib use in practice will be limited to the SmPC recommendation of no more than two 100g tubes per patient per month (6.57g).

EAG adjustments collectively reduce the expected incremental QALY gain associated with ruxolitinib while increasing its expected incremental cost, leading to EAG-preferred tentative ICERs that were far in excess of the relevant NICE decision-making threshold range, as results across Table 28, Table 29, Table 30 and Table 31 show. Figure 9 and Figure 10 serve to illustrate this point; in PSAs, all PSA iterations were above the £20,000 per QALY willingness to pay threshold. Mean probabilistic ICERs were higher than deterministic ICERs, owing to the skewed distribution of PSA iterations visible in Figure 9 and Figure 10. This trend was not present in the company's probabilistic analysis, and as such was likely attributable to EAG

correction #4, which incorporated variance-covariance matrices for utility regression analyses informing the company's health state utility assumptions into the cost-effectiveness model.

Table 28: From EAG-corrected company base case results to EAG-preferred tentative base case 1 results (all deterministic)

Preferred assumption	Section in EAG report	Cumulative ICER £/QALY
EAG-corrected deterministic company base case	6.1	*13,031*
Alignment of management costs with clinical practice – removal of vehicle cream and NB-UVB costs, removal of dermatology visits for patients in 'no response' and proportion of patients receiving psychological support set to 15% for all health states	6.2.1	*99,237*
Face validity of utility values – maximum utilities set to those of the general population and 'no response' utilities set to a weighted average of baseline and F-VASI50-74 values	6.2.2	*164,794*
Ruxolitinib dosing – assume pooled mean dose for only the ruxolitinib arms of TRuE-V studies	6.2.3	*302,651*
Duration of costs application in 'non-response' – set to lifetime	6.2.4	*301,699*
Approach to handling missing data for no regain of response – assume non-response	6.2.5	*303,189*

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 29: Summary EAG-preferred tentative base case 1 results

	Discounted costs (£)	Discounted QALYs	Δ discounted costs (£)	Δ discounted QALYs	ICER (£/QALY)
Deterministic					
Vehicle cream	[redacted]	[redacted]			
Ruxolitinib cream	[redacted]	[redacted]	[redacted]	[redacted]	303,189
Probabilistic					
Vehicle cream	[redacted]	[redacted]			
Ruxolitinib cream	[redacted]	[redacted]	[redacted]	[redacted]	329,105

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years

Figure 9: PSA scatterplot, EAG-preferred tentative base case 1

Abbreviations: EAG, External Assessment Group; PSA, probabilistic sensitivity analysis; QALYs, quality adjusted life years; WTP, willingness-to-pay

Table 30: From EAG-corrected company base case results to EAG-preferred tentative base case 2 results (all deterministic)

Preferred assumption	Section in EAG report	Cumulative ICER £/QALY
EAG-corrected deterministic company base-case	6.1	*13,031*
Alignment of management costs with clinical practice – removal of vehicle cream and NB-UVB costs, removal of dermatology visits for patients in 'no response' and proportion of patients receiving psychological support set to 15% for all health states	6.2.1	*99,237*
Face validity of utility values – maximum utilities set to those of the general population and 'no response' utilities set to a weighted average of baseline and F-VASI50-74 values	6.2.2	*164,794*
Ruxolitinib dosing – assume maximum dose according to SmPC recommendation for 2 x 100g tubes per patient per month	6.2.3	*262,543*
Duration of costs application in 'non-response' – set to lifetime	6.2.4	*261,592*
Approach to handling missing data for no regain of response – assume non-response	6.2.5	*262,880*

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 31: Summary EAG-preferred tentative base case 2 results

	Discounted costs (£)	Discounted QALYs	Δ discounted costs (£)	Δ discounted QALYs	ICER (£/QALY)
Deterministic					
Vehicle cream	[redacted]	[redacted]			
Ruxolitinib cream	[redacted]	[redacted]	[redacted]	[redacted]	262,880
Probabilistic					
Vehicle cream	[redacted]	[redacted]			
Ruxolitinib cream	[redacted]	[redacted]	[redacted]	[redacted]	283,278

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years

Figure 10: PSA scatterplot, EAG-preferred tentative base case 2

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

6.3.1. Scenario analyses around the EAG's preferred assumptions

Table 32: Individual impact of each scenario upon the EAG's and Table 36 present univariate scenario analyses around the EAG-preferred tentative base case results. The tables are a reflection of the exploratory analyses around the EAG-corrected company base case results

shown in Table 27, except around EAG-preferred results. They serve to illustrate the isolated importance of relaxing each of the EAG's proposed changes.

Table 32: Individual impact of each scenario upon the EAG's deterministic Base Case 1 ICER

Scenario	Section	Δ costs (£)	Δ QALYs	ICER (£/QALY)	+/- EAG base case
Base Case 1	-	[redacted]	[redacted]	303,189	-
Alignment of management costs with clinical practice – reverting to company assumptions	6.2.1	[redacted]	[redacted]	145,374	-157,815
Face validity of utility values – reverting to company assumptions	6.2.2	[redacted]	[redacted]	182,586	-120,603
Face validity of utility values – maximum utilities set to those of the general population and 'no response' utilities set to an arbitrary reduction of 5% from baseline utility values	6.2.2	[redacted]	[redacted]	361,765	+58,575
Ruxolitinib dosing – reverting to company assumptions	6.2.3	[redacted]	[redacted]	164,638	-138,551
Ruxolitinib dosing – assume a maximum recommended daily dose when two tubes per month	6.2.3	[redacted]	[redacted]	262,880	-40,310
Ruxolitinib dosing – assume a maximum recommended daily dose when two tubes per 28 days	6.2.3	[redacted]	[redacted]	284,996	-18,193
Duration of costs application in 'non-response' – reverting to company assumptions	6.2.4	[redacted]	[redacted]	304,141	+952
Duration of costs application in 'non-response' – alternative application based on lump sum	6.2.4	[redacted]	[redacted]	310,694	+7,505
Approach to handling missing data for no regain of response – reverting to company assumptions	6.2.5	[redacted]	[redacted]	301,699	-1,490
Retreatment with ruxolitinib set to 0%	6.2.6	[redacted]	[redacted]	350,808	+47,619

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 33: Individual impact of each scenario upon the EAG's deterministic Base Case 2 ICER

Scenario	Section	Δ costs (£)	Δ QALYs	ICER (£/QALY)	+/- EAG base case
Base Case 2	-	[redacted]	[redacted]	262,880	-
Alignment of management costs with clinical practice – reverting to company assumptions	6.2.1	[redacted]	[redacted]	105,064	-157,815
Face validity of utility values – reverting to company assumptions	6.2.2	[redacted]	[redacted]	158,311	-104,569
Face validity of utility values – maximum utilities set to those of the general population and 'no response' utilities set to an arbitrary reduction of 5% from baseline utility values	6.2.2	[redacted]	[redacted]	313,667	+50,788
Ruxolitinib dosing – assume pooled mean dose for only the ruxolitinib arms of TRuE-V studies	6.2.3	[redacted]	[redacted]	303,189	+40,310
Ruxolitinib dosing – reverting to company assumptions	6.2.3	[redacted]	[redacted]	164,638	-98,241
Ruxolitinib dosing – assume a maximum recommended daily dose when two tubes per 28 days	6.2.3	[redacted]	[redacted]	284,996	+22,117
Duration of costs application in 'non-response' – reverting to company assumptions	6.2.4	[redacted]	[redacted]	263,832	+952
Duration of costs application in 'non-response' – alternative application based on lump sum	6.2.4	[redacted]	[redacted]	270,384	+7,505
Approach to handling missing data for no regain of response – reverting to company assumptions	6.2.5	[redacted]	[redacted]	261,592	-1,288
Retreatment with ruxolitinib set to 0%	6.2.6	[redacted]	[redacted]	304,039	+41,159

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

In addition to the results presented in the tables above, multi-way sensitivity analyses around the tentative EAG-preferred base cases were performed for utility values, to establish the impact of jointly varying the utility values assumed for F-VASI90, F-VASI75-89, and 'non-response' health states. The details of and results from these analyses are reported in Appendix B.

6.4. Conclusions of the cost-effectiveness section

The EAG was not satisfied that the cost-effectiveness evidence submitted by the company addressed the decision problem at hand. The company's analysis used clinical effectiveness data from the previously treated subgroups of its pivotal registrational trials, and so addressed a subgroup of the licensed population and the final scope. This in itself was surmountable, if for example, the revised target population was considered identifiable and definable in guidance, although the EAG also noted the lack of comprehensive information about this subgroup presented in the CS (Key Issue 2). However, the cost-effectiveness comparison the company presented, to vehicle cream, was not appropriate for the proposed population. As such, the EAG did not find the company's model useful for addressing the decision problem the company proposed. The EAG considered that a comparison to vehicle cream, as a proxy for no active treatment, may only be appropriate for an end-of-line setting.

Furthermore, the EAG was not satisfied that the company's cost-effectiveness results provided an unbiased estimate of the likely cost-effectiveness of ruxolitinib. Most notably, the EAG identified: issues with the company's model logic and use of clinical effectiveness data (Key Issue 3); evidence that the company's dosing assumptions were underestimating expected ruxolitinib costs (Key Issue 4); indications that the company's preferred "non-response" state resource use assumptions overestimated healthcare costs (Key Issue 5); plausibility and internal consistency issues with the company's preferred health state utility estimates (Key Issue 6); an approach to capture adverse event consequences that underestimated cost and did not consider patient utility implications (Key Issue 7).

Within the timeframe of the EAG appraisal, the EAG was able to resolve some but not all of the Key issues identified. The EAG therefore present only "tentative" preferred results. These results, albeit tentative, did not suggest that the expected health benefits of ruxolitinib were sufficient to justify its expected incremental costs, given decision-making thresholds. This finding contrasted starkly with the company-preferred results.

Overall, the cost-effectiveness of ruxolitinib was highly uncertain. Substantial uncertainty could be resolved if the company addressed the outstanding Key Issues documented in this report.

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Appendix A: EAG indirect treatment comparison feasibility analysis

Table 34. EAG indirect treatment comparison feasibility analysis

	TRuE-V1[18]/TRuE-V2[19,32]	Thomas 2021 (HI-Light Vitiligo Trial){Thomas, 2021 #111	Eleftheriadou 2014[31]
	Inclusion / exclusion criteria		
Inclusion criteria	- Patients aged ≥ 12 years with a clinical diagnosis of nonsegmental vitiligo - Depigmented areas including ≥ 0.5% BSA on the face - ≥ 0.5 F-VASI - ≥ 3% BSA on nonfacial areas - ≥ 3 T-VASI - Total body vitiligo area (facial and nonfacial) was not to exceed 10% BSA	- Patients 5 years of age or over with a diagnosis of non-segmental vitiligo confirmed by a dermatologist. - Vitiligo limited to approximately 10% or less of body surface area, with at least one patch that is reported by the participant to have been active in the last 12 months. - No other active therapy for vitiligo (or willing to stop current treatment – no washout period required). - Able to administer the intervention safely at home	- Patients 5 years of age or over with a diagnosis of non-segmental vitiligo confirmed by a dermatologist. - Vitiligo affecting less than 25% or less of body surface area - No therapy for vitiligo in the previous two weeks and no other concurrent vitiligo treatments during the trial were allowed.
Exclusion criteria	- Other types of vitiligo - Patients who had no pigmented hair within any of the vitiligo areas on the face. - Patients who had used depigmentation treatments (e.g., monobenzone) - Any other skin disease that would interfere with the study medication application or study assessments - Any serious illness or medical, physical, or psychiatric condition(s) that would interfere with full participation in the study	- Other types of vitiligo (e.g. segmental or universal vitiligo). - History of skin cancer - History of radiotherapy use - Photosensitivity - Current use of immunosuppressive drugs	- Segmental or universal Vitiligo - Previous history of skin cancer - Recent/concurrent radiotherapy - Photosensitivity - Use of immunosuppressive or photosensitive drugs
	Actual distribution of demographics/disease characteristics between sources		

	TRuE-V1[18]/TRuE-V2[19,32]		**Thomas 2021 (HI-Light Vitiligo Trial){Thomas, 2021 #111**			**Eleftheriadou 2014[31]**	
Treatment arm	Ruxolitinib cream	Placebo (vehicle cream)	Placebo device with TCS	NB-UVB with placebo cream	NB-UVB with TCS	NB-UVB	Placebo device
Number of patients	450	224	173	169	175	19	10
Mean (SD) Age in years	39.5 (15.38)	39.7(14.5)	38.6 (20.0)	36.9 (18.9)	37.0 (19.1)	27.6 (18.6)	39.4 (13.5)
Min, max	12, 79	12, 79	NR	NR	NR	5, 71	13, 51
Sex, n (%)							
Male	202 (44.9)	114 (50.9)	75 (43.3)	88 (52.1)	105 (60.0)	10 (52.6)	5 (50.0)
Female	248 (55.1)	110 (49.1)	98 (56.6)	81 (48.0)	70 (40.0)	9 (47.4)	5 (50.0)
Fitzpatrick skin type, n (%)							
I	12 (2.7)	4 (1.8)	2 (1.2)	2 (1.2)	5 (2.9)	NR	NR
II	131 (29.1)	72 (32.1)	31 (17.9)	32 (18.9)	29 (10.9)	NR	NR
III	179 (39.8)	88 (39.3)	70 (40.4)	66 (39.1)	59 (19.4)	NR	NR
IV	89 (19.8)	40 (17.9)	29 (16.8)	34 (20.1)	33 (18.9)	NR	NR
V	28 (6.2)	17 (7.6)	35 (20.2)	25 (14.8)	44 (25.1)	NR	NR
VI	11 (2.4)	3 (1.3)	6 (3.5)	10 (5.9)	10 (5.7)	NR	NR
Race, n (%)							
White	363 (80.7)	189 (84.4)	112 (64.7)	114 (67.5)	104 (59.4)	12 (63.2)	8 (80.0)
Black/African American	23 (5.1)	9 (4.0)	5 (2.9)	3 (1.8)	7 (4.0)	2 (10.5)	0
Asian	17 (3.8)	11 (4.9)	36 (20.8)	39 (23.1)	49 (28.0)	3 (15.8)	2 (20.0)
American Indian/Alaska Native	2 (0.4)	0	NR	NR	NR	NR	NR
Native Hawaiian/Pacific Islander	2 (0.4)	0	NR	NR	NR	NR	NR
Mixed race	NR	NR	9 (5.2)	6 (3.6)	6 (3.4)	1 (5.3)	0

	TRuE-V1[18]/TRuE-V2[19,32]		Thomas 2021 (HI-Light Vitiligo Trial){Thomas, 2021 #111			Eleftheriadou 2014[31]	
Not reported	19 (4.2)	6 (2.7)	1 (0.06)	0	1 (0.06)	0	0
Other	24 (5.3)	9 (4.0)	10 (5.8)	7 (4.1)	9 (5.1)	1 (5.3)	0
Years since initial diagnosis of vitiligo							
Mean (SD)	14.9 (11.9)	14.6 (11.0)	NR	NR	NR	11.4 (10.1)	14.0 (8.5)
Median (IQR)	11.8	12.1	7 (3-16)	5 (3–11)	7 (4–15)	NR	NR
Disease status, n (%)							
Stable	331 (73.6)	168 (75.0)	NR[a]	NR[a]	NR[a]	5 (26.3) – ‘stable’ or ‘repigmenting’	5 (50.0) – ‘stable’ or ‘repigmenting’
Progressive	119 (26.4)	56 (25.0)	NR[a]	NR[a]	NR[a]	14 (76.7) – “spreading”	5(50.0) – “spreading”
T-BSA involvement							
Mean (SD)	7.36 (2.0)	7.46 (2.0)	NR	NR	NR	9.8 (6.0)	6.9 (6.2)
Prior therapy received, n (%)							
Topical corticosteroids	133 (29.6)	56 (25.0)	80 (46.2)	75 (44.4)	80 (45.6)	NR	NR
Topical calcineurin inhibitor	146 (32.4)	68 (30.4)	51 (29.5)	39 (23.1)	56 (32.0)	NR	NR
NB-UVB	138 (30.7)	77 (34.4)	28 (16.2) received “light therapy”	26 (15.4) received “light therapy”	37 (21.1) received “light therapy”	NR	NR
Outcomes							
Patient reported vitiligo scales	Patient reported VNS at 24 weeks and 52 weeks (5 point scale)		Patient reported VNS at 9 months.			Global improvement in vitiligo: 5-point Likert scale	
Repigmentation	T-VASI75[b] / F-VASI75[b] at 24 weeks and 52 weeks		≥ 75% repigmentation at 9 months on the “target patch”			≥ 75% repigmentation at 16 weeks in up to 3 target lesions per patient	

[a] The study had an inclusion criteria was having a vitiligo patch that was reported as active (new or changed). Thus, it would appear all participants has progressive vitiligo.

[b] T-VASI75/F-VASI75: achieving at least 75% improvement from baseline.

Abbreviations**:** BSA, body surface area; F-VASI, face vitiligo area scoring index; SD, standard deviation; T-BSA, total body surface area; TCI, topical calcineurin

Appendix B: Multi-way sensitivity analysis of utility values

As noted in Section 6.2.2, there is substantial uncertainty concerning the estimation of utility values to populate the company's model. Given the differences between the company's preferred utility values and the EAG's preferred utility values (see Section 6.2.2), a further multi-way analysis was conducted. In the multi-way sensitivity analysis:

- The company's preferred utility values were considered upper limits, whereas the EAG's preferred values were considered lower limits.
- Utility for 'no response' was varied between 0.797 and 0.822, in increments of ~0.003. Please note that the value of 0.822 (and by extension the increment of ~0.003) was edited following the factual accuracy check stage of this appraisal.
- Utility for 'F-VASI75-89' was varied between 0.908 to 0.935, in increments of ~0.003.
- Utility for 'F-VASI90' was varied between 0.908 to 0.945, in increments of ~0.004.
- The increments between the bounds were determined based on the difference between the bounds divided by nine, meaning that a total of 10 different utility values can be explored.
- The utility values for F-VASI75-89 and F-VASI90+ were varied at the same time, such that a 10x10 table of ICERs using different combinations of utility values could be produced.

The results of this analysis are presented in Table 35 for Base Case 1. In this table, the bottom-left ICER refers to the EAG's preferred utility values (ICER = £303,189 for Base Case 1), whereas the top-right ICER refers to the company's preferred utility values (ICER = £182,586 for Base Case 1). The same table is re-produced for Base Case 2 in Table 36. Ultimately, the multi-way sensitivity analysis demonstrates the extent to which the cost-effectiveness results of the model vary when changing between the company's and EAG's preferred utility values for the different model health states. Given the magnitude of QALYs gain in absolute terms, relatively small changes in utility values can have a profound impact on the ICER.

Table 35: Multi-way sensitivity analysis of utility values (aligned to tentative EAG-preferred base case 1) – ICER for ruxolitinib versus vehicle cream

Utility value for…		Utility value for 'No response'									
…F-VASI75-89	**…F-VASI90**	**0.822**	**0.819**	**0.816**	**0.814**	**0.811**	**0.808**	**0.805**	**0.803**	**0.800**	**0.797**
0.935	**0.945**	£221,221	£216,139	£211,286	£206,646	£202,205	£197,951	£193,873	£189,959	£186,200	**£182,586†**
0.932	**0.941**	£228,072	£222,675	£217,527	£212,612	£207,914	£203,419	£199,114	£194,988	£191,029	£187,228
0.929	**0.937**	£235,361	£229,618	£224,148	£218,932	£213,954	£209,197	£204,647	£200,291	£196,117	£192,112
0.926	**0.933**	£243,132	£237,007	£231,184	£225,640	£220,356	£215,314	£210,497	£205,891	£201,482	£197,258
0.923	**0.928**	£251,432	£244,889	£238,677	£232,772	£227,153	£221,798	£216,691	£211,813	£207,150	£202,687
0.920	**0.924**	£260,320	£253,312	£246,671	£240,370	£234,382	£228,686	£223,260	£218,085	£213,145	£208,424
0.917	**0.920**	£269,859	£262,336	£255,220	£248,480	£242,087	£236,015	£230,240	£224,741	£219,498	£214,494
0.914	**0.916**	£280,124	£272,026	£264,382	£257,157	£250,316	£243,829	£237,670	£231,815	£226,241	£220,929
0.911	**0.912**	£291,201	£282,459	£274,227	£266,461	£259,123	£252,179	£245,596	£239,349	£233,412	£227,762
0.908	**0.908**	**£303,189***	£293,725	£284,834	£276,465	£268,573	£261,120	£254,069	£247,389	£241,052	£235,031

Abbreviations: F-VASI, Facial Vitiligo Area Scoring Index; ICER, incremental cost-effectiveness ratio.

Note: *EAG Base Case 1 – see Table 29; †EAG Base Case 1 with utility values as per Company's preferred assumptions – see Table 32.

Table 36: Multi-way sensitivity analysis of utility values (aligned to tentative EAG-preferred base case 2) – ICER for ruxolitinib versus vehicle cream

Utility value for…		Utility value for 'No response'									
…F-VASI75-89	**…F-VASI90**	**0.822**	**0.819**	**0.816**	**0.814**	**0.811**	**0.808**	**0.805**	**0.803**	**0.800**	**0.797**
0.935	**0.945**	£191,809	£187,403	£183,195	£179,172	£175,321	£171,633	£168,097	£164,703	£161,444	**£158,311†**
0.932	**0.941**	£197,749	£193,070	£188,606	£184,344	£180,271	£176,374	£172,642	£169,064	£165,632	£162,336
0.929	**0.937**	£204,069	£199,089	£194,347	£189,825	£185,508	£181,384	£177,439	£173,662	£170,042	£166,571
0.926	**0.933**	£210,807	£205,497	£200,448	£195,641	£191,059	£186,687	£182,511	£178,517	£174,695	£171,032
0.923	**0.928**	£218,004	£212,330	£206,944	£201,825	£196,952	£192,310	£187,881	£183,652	£179,609	£175,740
0.920	**0.924**	£225,710	£219,634	£213,876	£208,412	£203,221	£198,282	£193,577	£189,090	£184,807	£180,713
0.917	**0.920**	£233,981	£227,457	£221,288	£215,444	£209,901	£204,636	£199,629	£194,861	£190,315	£185,977
0.914	**0.916**	£242,881	£235,859	£229,232	£222,967	£217,036	£211,411	£206,071	£200,995	£196,162	£191,556
0.911	**0.912**	£252,485	£244,906	£237,768	£231,035	£224,672	£218,651	£212,944	£207,527	£202,379	£197,480
0.908	**0.908**	**£262,880***	£254,673	£246,964	£239,708	£232,866	£226,404	£220,290	£214,498	£209,003	£203,783

Abbreviations: F-VASI, Facial Vitiligo Area Scoring Index; ICER, incremental cost-effectiveness ratio.

Note: *EAG Base Case 2 – see Table 31; †EAG Base Case 2 with utility values as per Company's preferred assumptions – see Table 33.

Single Technology Appraisal

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

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 25 October 2023** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 The clinical and cost effectiveness of ruxolitinib as compared to established treatment options is unknown

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG make the following statement on pg 14: *"The EAG considered that a comparison with vehicle cream was only relevant for the end of the treatment pathway; i.e. after all other treatment options have been considered. However, the company stated that the appropriate positioning for ruxolitinib would be at the 2nd line position, between the use of TCS/TCIs and NB-UVB therapy. Clinical advice to the EAG was also that a 2nd line position would be more appropriate for ruxolitinib. However, the EAG did not consider that the CS was consistent with this positioning."*	The company would like the statement to be amended as follows: *"The company stated that the appropriate positioning of ruxolitinib cream would be as a step change option between first and second line, for adults and adolescents from 12 years of age with NSV with facial involvement for whom the disease has not responded to TCS, TCI, or for whom TCS or TCI are contraindicated, not tolerated or otherwise medically inadvisable. This positioning is aligned with clinical advice to the EAG. Therefore, vehicle cream is the relevant comparator in this positioning".*	The company does not agree with the claim that a comparison with vehicle cream was only relevant for the end of the treatment pathway, after all other treatment options have been considered. Ruxolitinib cream is anticipated to be positioned as a step change option between first and second line for adults and adolescents from 12 years of age with NSV with facial involvement for whom the disease has not responded to TCS, TCI, or for whom TCS or TCI are contraindicated, not tolerated or otherwise medically inadvisable. This positioning is aligned with clinical advice to the EAG and to the company (pg 14). Specifically, the company notes the following (pg 26): *"The EAG therefore did not disagree with the company's proposed positioning, but rather considered that the evidence base*	The EAG does not consider this to be a matter of factual inaccuracy. The positioning and corresponding comparator is a matter for the committee to discuss. While the company may disagree with the EAG, this does not constitute a factual inaccuracy. No change has been made to the EAR.

		submitted by the company was not appropriate for decision-making in this position." As highlighted by the company in responses to clarification questions, in patients with vitiligo whose disease has not responded to initial treatment with TCS or TCI, the current BAD guidelines recommend offering either NB-UVB +/- TCS or TCI, or considering oral betamethasone specifically for rapidly progressive disease[1]. Neither of these options are appropriate comparators for the appraisal of ruxolitinib cream for the following reasons: A retrospective cohort study amongst vitiligo patients in the UK found that among the prevalent cohort of 44,910 patients in 2019, 85.0% of patients were not on vitiligo-related treatment. In the first year after diagnosis, 60.8% of patients did not receive any vitiligo-related treatment (e.g., topical steroids, topical calcineurin inhibitors, oral steroids, phototherapy), increasing to ≥82.0% from the second year onward. This finding is indicative of	

		the vast majority of prevalent patients, including those with prior failure with TCS or TCI, not proceeding to another line of off-label therapy. In the first year, patients were recorded as having been prescribed topical corticosteroids (29.1%), topical calcineurin inhibitors (11.8%), and oral corticosteroids (4.2%). From the second year onward, the percentage of patients prescribed oral corticosteroids remained stable, while prescription of topical corticosteroids and calcineurin inhibitors declined to 11.4% and 3.9% in the second year, respectively, remaining low thereafter[2]. Introduction of a topical treatment after failure of initial topical treatment but prior to phototherapy is less burdensome for patients with vitiligo and less of a strain on NHS resources. Furthermore, there remains a lack of equitable access to phototherapy, which is further compounded by other competing chronic inflammatory skin disease indications for phototherapy such as psoriasis and atopic dermatitis, resulting in	

		long wait times and variability in receiving this treatment option across the UK. Finally, and more fundamentally, clinicians generally recommend that phototherapy is prioritised for patients with large BSA (i.e., >10%) affected[3,4]. Please refer to Key Issue 2 below for further detail on the clinical evidence provided as part of the submission.	
The EAG make the following statement on pg 14: The EAG has misrepresented the company. *"At clarification (question B1), the EAG requested that the company re-formulate their economic evaluation to represent a specific position in the treatment pathway, i.e., to compare ruxolitinib with the existing treatment options that it would displace. The company declined to do this*."	The company would like the statement to be amended as follows: *"At clarification (question B1), the EAG requested that the company re-formulate their economic evaluation to represent a specific position in the treatment pathway, i.e., to compare ruxolitinib with the existing treatment options that it would displace. The company stated in their clarifications that the anticipated positioning that comparisons against TCS/TCI or phototherapy were neither appropriate for the anticipated pathway positioning, nor possible given the infeasibility of robust indirect comparisons*."	The company asserts that this statement is factually inaccurate as this approach was agreed with the EAG during discussion of clarification questions on the 1st September 2023. The company reiterate that neither TCS/TCI nor phototherapy are appropriate comparators for this position. Given the lack of treatment alternatives in the anticipated positioning, the company considers that vehicle cream as investigated in the double-blind phase of the TRuE-V trials is an comparator for the appraisal of ruxolitinib cream. The EAG acknowledge the infeasibility of robust indirect	The EAG does not consider this to be a matter of factual inaccuracy. This request was made at the clarification stage of the appraisal, and the company declined to provide the analysis requested. The EAG does not recall any agreement with the company that could be construed as withdrawing the request made in the clarification question. The EAG acknowledges the company's rationale for declining to provide the requested analysis, but it nevertheless remains true that the company declined to

		comparisons against off-label treatments in pathway positions other than the one anticipated for ruxolitinib cream (pg 77).	provide the analysis. The EAG has therefore not misrepresented the company. No change has been made to the EAR.
The EAG make the following statement on pg 14: *"It was not possible for the EAG to comment on the likely magnitude of effect on the ICER in the absence of any evidence for alternative comparators and in consideration of the broader structural issues with the company's model…"*	The company would like the statement to be amended as follows: *"It was not possible for the EAG to comment on the likely magnitude of effect on the ICER due to the infeasibility of robust comparisons with alternative comparators and in consideration of the broader structural issues with the company's model…"*	The company provided an ITC feasibility assessment based on evidence retrieved from a comprehensive systematic literature review, concluding that robust ITC was infeasible versus off-label treatments in pathway positions different from the one anticipated for ruxolitinib cream. The EAG also confirm in their report (pg 77) that a robust comparison with potential comparators was not feasible. The EAG further note that *"the company should have conducted a head-to-head trial to compare ruxolitinib with the alternative treatment options at its proposed positioning…".* The company note that apart from these alternatives not being appropriate comparators for the anticipated positioning, an RCT versus phototherapy would	Thank you for this comment, the EAG agree that the proposed amendment is clearer. The EAG has therefore made the following edit to the EAR (p.14): *"It was not possible for the EAG to comment on the likely magnitude of effect on the ICER due to the infeasibility of robust comparisons using available evidence for alternative comparators and in consideration of the broader structural issues with the company's model…"*

		be infeasible due to the impossibility of blinding.	
The EAG make the following statement on pg *15:* *"The company should have performed a narrative synthesis of evidence for the different treatment options, to consider the relative effectiveness of treatment options in consideration of variation in trial design"*	The company perform a feasibility analysis of existing treatment for vitiligo – to consider the relative effectiveness of treatment options but found that a comparison was not feasible. The paragraph should be amended as follows: *"Due to the infeasibility of conducting a robust indirect comparison, the company did not perform a narrative synthesis of evidence for the different treatment options; the EAG considered this reasonable."*	The EAG acknowledge that robust indirect comparisons are infeasible (pg 77):*"using either an NMA or a MAIC was not feasible and/or would not be useful for decision-making".* As such, a narrative synthesis of evidence would not be useful or appropriate to inform statements about relative efficacy for consideration in the economic evaluation.	The EAG does not consider this to be a matter of factual inaccuracy. The statement referenced constitutes an opinion of the EAG, and that in spite of the evidence base having its limitations, the EAG considered that it would have been useful to see a narrative synthesis from the company. The EAG does not consider the lack of comment about the reasonableness of omitting an analysis to be factually inaccurate. No change has been made to the EAR.
The EAG make the following statement on pg 15: *"Overall, the EAG considered that the CS presented by the company undermined the ability of the EAG to conduct a full appraisal of the clinical effectiveness evidence for ruxolitinib*."	The company would like the paragraph to be updated to the following: *"The EAG received the necessary information to enable the conduct of a full appraisal of the clinical effectiveness evidence for ruxolitinib cream."*	The company worked with EAG to prioritise data requested in the clarification questions engagement (on 1st September 2023) and with agreement from EAG provided the necessary information for the assessment	The EAG does not consider this to be a factual inaccuracy. As part of the NICE HTA process, manufacturers are required to submit the evidence relevant to the decision problem in a prepared submission template. The

			key evidence relevant to decision making should be contained within Document B of this template, with additional supplementary information relevant to the appraisal by the EAG provided in structured appendices. The company submission template omitted key information relevant to the decision problem for this appraisal. Information relevant to the appraisal was supplied across various additional files that would not be accessible to the public and would not be routinely supplied to the NICE committee. This included series of poorly labelled excerpts from trial CSRs that contained large amounts of irrelevant information. Within the timeline of the appraisal, the EAG could not confirm that all relevant information had been supplied by the company or appraise the evidence relevant to the decision problem in depth. The EAG therefore

			concluded that the company submission lacked transparency. No change has been made to the EAR.
The EAG make the following statement on pg 26: *"Moreover, the EAG did not consider that the company had provided evidence or rationale to conclude that the same factors influencing treatment use would not also affect ruxolitinib (and so ruxolitinib would not be a realistic treatment option for those not currently receiving treatment)."*	The company suggests replacing the text with the following: *"The EAG did not agree with the rationale to conclude that the same factors influencing treatment use would not also affect ruxolitinib cream"*	Clinical advice to the EAG was that many people with vitiligo may not be receiving treatment. Clinical advice to the EAG was that this may be due to frustration with long waiting lists to see a consultant about their condition. The EAG suggest that as ruxolitinib was expected to be prescribed by a consultant, uptake of ruxolitinib would be similarly affected, and that ruxolitinib would not therefore offer an alternative treatment option for this group. As stated in the CS, once seen in secondary care, many patients with vitiligo are unable to start phototherapy either due to long NHS waiting lists (over one year at some centres, following first assessment by a dermatologist) for this treatment option, and/or personal time constraints (i.e., the need to attend three times a week for 9-12 months). Furthermore,	The EAG does not consider this to be a factual inaccuracy. The statement quoted by the company is the view of the EAG on the basis of the evidence presented by the company. No change has been made to the EAR.

		many dermatology departments offer phototherapy to a small cohort of patients with vitiligo due to the prolonged course of treatment. As such, patients with other dermatological diseases (such as eczema or psoriasis) who usually require shorter courses are prioritised instead[5]. These limitations that impact access to phototherapy for patients with vitiligo do not affect access to ruxolitinib cream, which is a topical treatment that does not require a hospital visit.	

Issue 2 The clinical effectiveness evidence presented by the company was not representative of the target population and the population used in the company's economic evaluation

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG make the following statement on pg 16: *"As the EAG had not received a full submission for this population (including population characteristics including the prevalence of effect modifiers) and could not compare this finding across outcomes, the EAG was*	The company would like the statement to be amended as follows: *"As the EAG did not review the provided evidence for this population within the timeline available, the EAG was unsure if this was evidence of a true*	The necessary analyses were provided by the company to support assessment by the EAG. Please refer to the document that was provided together with responses to clarification questions, named "A2. subgroup data using NRI and LOCF".	The EAG does not consider this to be a matter of factual inaccuracy. The company did not provide the population characteristics of the previously treated subgroup at clarification. Moreover, the "A2. subgroup data using NRI and LOCF"

unsure if this was evidence of a true difference in treatment effect between treatment lines."	*difference in treatment effect between treatment lines."*		folder provided by the company was a set of excerpts that appeared to be taken from the CSRs of the TRuE-V1 and TRuE-V2 trials and were insufficiently labelled to allow critique by the EAG. No change has been made to the EAR.
The EAG make the following statement on pg 28: "…*the EAG did not consider that the company had provided evidence or rationale to determine whether ruxolitinib would be used by people who were not accessing existing treatments"*	The company would like the statement to be amended as follows: *"The EAG did not agree with the rationale provided by the company to determine whether ruxolitinib cream would be used by people who were not accessing existing treatments"*	The company considered RWE sources – VALIANT and REVEAL-UK regarding the possibility of patients not seeking treatment[2,6]. As the first licensed treatment for NSV, ruxolitinib cream addresses an unmet need by offering a tolerable and effective treatment for what has to date been a chronically neglected and underserved patient population.	The EAG does not consider this to be a factual inaccuracy. The EAG maintains the view that the company did not provide convincing rationale or evidence to substantiate this point. No change has been made to the EAR.
The EAG make the following statement on pg 33: *"though noted that the comparison reported was different to that the company stated was requested in the decision problem meeting (the company presented a comparison*	The company suggests that this claim is removed as it is factually incorrect.	The company stresses that this claim is factually incorrect. Although patients were stratified according to Fitzpatrick skin type (I-II vs III-VI) in the TRuE-V1/2 trials, the company provided an analysis using the subgroups Fitzpatrick	The EAG does not consider this to be a matter of factual inaccuracy. The subgroup analysis presented in Document B (Section B.2.7) used a comparison between Fitzpatrick scale Type I/II and Type III/IV/V/VI).

between Fitzpatrick scale Type I/II and Type III/IV/V/VI).”		skin type I-III vs IV-VI, presented in Appendix M.	Appendix M does link to a spreadsheet that contains outcome data for the Fitzpatrick skin type I-III and IV-VI subgroups. However, no formal subgroup analysis was presented in the CS. No change has been made to the EAR.
The EAG make the following statement on pg 36: *“No meta-analysis or narrative synthesis was undertaken.”*	The company would like the statement to be amended as follows: *“The company did perform a feasibility analysis of existing treatment for vitiligo – to consider the relative effectiveness of treatment options but found that a comparison was not feasible*”	The company conducted an ITC feasibility assessment which found that there is an insufficient evidence base to robustly compare the efficacy of ruxolitinib cream to existing off-label therapies. Details of this were presented in Appendix D, and the company provided the ITC feasibility assessment report together with responses to clarification questions. Furthermore, EAG drew the same conclusion as the company when they did their own assessment (section 3.4.1-3.4.2 EAG report).	The EAG does not consider this to be a factual error. The EAG note the company’s feasibility analysis in the appropriate section within the report, and the statement quoted by the company is correct. No change has been made to the EAR.
The EAG make reference to the following on pg 40: INCB 18424-211 (Table 7).	The company suggest that reference to the INCB 18424-211 study on Table 7 is removed	Both the CSR and protocol for the Phase 2 INCB 18424-211 study were provided to the EAG together with responses to the clarification questions.	The EAG does not regard this as a factual error. The results if INCB 18424-211 were not provided in the CS and it was not clear after

			clarification why it was not included in the SLR. No change has been made to the EAR.
The EAG make the following statement on pg 43: *"One limitation of the trials was that evidence was not collected to determine the effectiveness of repeat treatments with ruxolitinib."*	The company would like the statement to be updated as follows: *"A limitation of the trials was that evidence was collected to determine the effectiveness of only one round of repeat treatment with ruxolitinib cream*"	TRuE-V LTE reports efficacy after one round of re-treatment to regain response (≥ F-VASI90)[7,8].	Thank you for this comment. The EAG have replaced the quoted statement in the EAR with the following: (p.43) "The TRuE-V-LTE trial reports treatment efficacy after one round of re-treatment with ruxolitinib in those with a high level of response (F-VASI90). However, a limitation of the trials is that the efficacy of retreatment for those with a lower prior response was not captured, nor was the efficacy of multiple rounds of re-treatment.
The EAG make the following statement on pg 43: *"Specifically, as discussed in Section* ***Error! Reference source not found.****, the trials were unlikely to capture the risk of nonmelanoma skin cancer."*	The company suggests adding the following: "*However, as stated in EPAR (Appendix C), the ongoing PASS (INCB88888-037) study evaluates the safety of long-term ruxolitinib cream use with respect to*	The trials were unlikely to capture the risk of nonmelanoma skin cancer. However, as stated in EPAR[9] (Appendix C), the PASS (INCB88888-037) study will evaluate the safety of long-term ruxolitinib cream use with respect to incidence of non-melanoma skin	The EAG does not consider this to be a factual inaccuracy. Throughout the EAR, the EAG refer to the trials in relation to the evidence presented by the company in the CS. As noted in Section 3.2.1,

	incidence of non-melanoma skin cancers."	cancers. The protocol will be submitted within 6 months of EC decision and final report should be available in 2030 (interim reports from 2026-2029).	during its appraisal the EAG became aware of three ongoing trials of ruxolitinib that were not described in the CS. Section 3.2.3.1, mentioned in the quoted statement in the EAR, reports the clinical effectiveness results from trials that were presented to the EAG.
The EAG make the following statement on pg 44: *"The EAG was unclear to what extent the missing data was due to drop-out from the trial or whether a number of participants did not meet the company's criteria for entry (i.e. no safety concerns with continuing ruxolitinib)."*	The company would like this statement to be removed.	No safety concerns were observed with the use of ruxolitinib cream. As presented in Table 23 in document B, in the pooled TRuE-V1 and TRuE-V2 ITT population, only two patients had a treatment emergent adverse event that led to study drug discontinuation[9]. Primary reasons for treatment discontinuation are presented in the patient disposition in TRuE-V1 and TRuE-V2 (Figure 6 in document B) and Table 1.1.2.2 in the TRuE-V1 and TRuE-V2 CSRs[9-11].	The EAG does not consider this to be a matter of factual inaccuracy. The statement on page 44, quoted by the company, is referring to a lack of clarity about missing data in the TruE-V-LTE trial. No change has been made to the EAR.
The EAG make the following statement on pg 48: *"Based on the evidence presented by the EAG, it was not possible to*	The company suggest replacing the text with the following: *"The proportion of participants in the TRuE-V1/2 trials for whom the*	This information was presented in Table 8 in document B. The information is also presented in Table 19 in EPAR[9] and is	The EAG does not consider this to be a matter of factual inaccuracy. Table 1 in Rosmarin D et al (2022) and

determine the proportion of participants in the trials for whom the disease had not responded to TCS and/or TCI, or for whom TCS or TCI were contraindicated, not tolerated or otherwise medically inadvisable."	*disease has not responded to TCS, TCI, or for whom TCS or TCI are contraindicated, not tolerated or otherwise medically inadvisable is presented in Table 1 in the Rosmarin D et al, 2022. TRuE-V1/2 publication"*	published in Table 1 in the Rosmarin D et al, 2022 TRuE-V1/2 publication[12].	Table 19 in the EPAR report the demographic and clinical characteristics of the participants in the TRuE-V1 and TRuE-V2 trials. Within the tables it indicates the number of participants who had previously received TCS or TCIs. However, it did not report the number of participants who had not responded to TCS and/or TCI, or the number for whom TCS or TCI were contraindicated or otherwise medically inadvisable. The statement in the EAR is therefore correct. No change has been made to the EAR.
The EAG make the following statement on pg 49: *"The safety implications of higher ruxolitinib doses were also unclear."*	The company consider that this statement should be removed as it is not accurate.	The safety of ruxolitinib cream was assessed by the EMA and MHRA[9,13]. It is not appropriate for the EAG to make judgements on the safety of ruxolitinib 1.5% cream without aligning to the recommendations of the EMA and MHRA.	The EAG does not consider this to be a matter of factual inaccuracy. The statement taken from page 49 of the report refers to the safety of higher doses than the highest dose evaluated in the ruxolitinib trials. The EAG is not making a judgement about the safety of ruxolitinib at higher doses

			but stating that, given the doses tested, it is currently unclear. No change has been made to the EAR.
The EAG make the following statement on pg 58: "*Some data required by the NICE decision problem were only available in trial CSR documents and appendices. Notably, this included clinical effectiveness outcome data for the previously treated subgroup, which were not in the CSR documents provided by the company (though the EAG requested that all CSR files, including tables and appendices be submitted [clarification question C2]) but were submitted by the company in a series of files at clarification that appeared as if they were originally an appendix to the CSRs. These were poorly labelled, which led to uncertainty about the data source."*	The company would like to amend this statement as follows: *"The company shared the CSRs for TRuE-V1, TRuE-V2 and TRuE-V LTE, in addition to EPAR, to help provide the data required by the NICE decision problem. Further, the company provided subgroup data that was requested by the EAG as part of clarification questions. However, the EAG did not review this data within the timelines available"*	In addition to the CSRs for TRuE-V1, TRuE-V2 and TRuE-V LTE, the necessary analyses were provided by the company to support assessment by the EAG. Please refer to the document that was provided together with responses to clarification questions, named "A2. subgroup data using NRI and LOCF".	The EAG does not consider this to be a matter of factual inaccuracy. As detailed in response to a previous item, the EAG considered that the company submission omitted key information from the submission template and that the presentation of data in attached files lacked transparency. No change has been made to the EAR.
The EAG make the following statement on pg 71:	. The company would like to amend the statement as follows:	The necessary data and analyses were provided by the company to support assessment by the EAG.	The EAG does not consider this to be a factual inaccuracy. As detailed in a

"Data for some outcomes was provided for trial participants who had previous received treatment at clarification (question C2). These data appeared to be excerpts from the appendices of the trial CSRs, though these tables were not provided to the EAG in the appendices of CSRs provided earlier in the appraisal (though these and all data tables were requested by the EAG)."	*"Subgroup data for outcomes was provided for trial participants who had previously received treatment during clarification."*	Please refer to CSRs and to the document that was provided together with responses to clarification questions, named "A2. subgroup data using NRI and LOCF". The EAG stated that they did not review the provided evidence for this population within the timeline available, please refer to page 71: *"Within the timeframe of the appraisal, it was not possible for the EAG to review all these documents."*	previous item and in the preceding item, the EAG considered that the company submission lacked transparency as evidence relevant to the decision problem was not provided within the submission template and was provided in a format that lacked transparency. No change has been made to the EAR.
The EAG make the following statement on pg 77: *"The EAG considered that the effectiveness of ruxolitinib in the subgroup of people who had previously received treatment was uncertain. The EAG had no evidence to believe that treatment effects would be different in those who had previously received treatment, however considered that an appraisal of these data would be useful to reduce this uncertainty"*	The company suggest that the text is updated to the following: *"As the EAG did not review the provided evidence for the subgroup of people who had previously received treatment within the timeline available, the EAG considered that the effectiveness of ruxolitinib cream in this subgroup is uncertain. The EAG had no evidence to believe that treatment effects would be different in those who had previously received treatment, however considered that an*	The necessary analyses were provided by the company to support assessment by the EAG. Please refer to the document that was provided together with responses to clarification questions, named "A2. subgroup data using NRI and LOCF". The EAG stated that they did not review the provided evidence for this population within the timeline available, please refer to page 71: *"Within the timeframe of the appraisal, it was not possible for the EAG to review all these documents."*	The EAG does not consider this to be a factual inaccuracy. As stated in response to the previous items, the company did not provide all evidence relevant to this appraisal within the submission template and the EAG considered that the presentation of data in supplementary files lacked transparency. This created uncertainty in the appraisal as the EAG was unable to appraise these data in the normal way.

	appraisal of these data would be useful."		No change has been made to the EAR.

Issue 3 Cost-effectiveness model's structural assumptions and use of clinical effectiveness data

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG make the following statement on pg 17: *"The company's chosen model structure assumed that patients who achieve F-VASI50-74 at ~24 weeks discontinue treatment owing to non-response. This is neither in line with expectations for clinical practice nor in line with the company's own registrational trials."* *The EAG also make the following comment on pg 111:* *"The company appeared to have selectively used advice from these meetings. For example, the questions put to the clinical experts on response definitions and answers received across each clinical expert acknowledged the*	The company would like to request the text on pg 17 be amended as follows: *"The company's chosen model structure assumed that patients who achieve F-VASI50-74 at 24 weeks discontinue treatment owing to non-response. This is line with the primary endpoint of the TRuE-V studies."* The company request the EAG to update the statement on pg 111 to the following: *"The EAG notes that the advice received by the company regarding initial response definition was not consistent and recognize that the model was aligned with the primary endpoint of the TRuE-V studies"*	The modelled definition of non-response at week 24 was based on the primary endpoint of the TRuE-V studies (F-VASI75)[10,11]. Initial response in the model is assessed at week 24 in line with the TRuE-V studies. Clinicians agreed that aligning the modelled definition of non-response at week 24 with the TRuE-V studies was reasonable[3].	The EAG does not consider this to be a factual inaccuracy. The statements are representative of the EAG's appraisal. No change has been made to the EAR.

clinical relevance of VASI50 at 24 weeks."			
The EAG make the following statement on pg 84: *"Given the company's proposed positioning, EAG clarification question B1 (marked "Priority") asked the company to respecify the cost-effectiveness comparison at an appropriate point in the treatment pathway, with appropriate comparators. As documented in section* ***Error! Reference source not found.*** *of this report, the company declined to do so."*	The company suggest that the text be updated to the following: *"Given the company's proposed positioning, EAG clarification question B1 (marked "Priority") asked the company to respecify the cost-effectiveness comparison at an appropriate point in the treatment pathway, with appropriate comparators. In response, the company restated their target reimbursement population and positioning, as well as non-feasibility of ITC."* The company also requests that text in section 2.4 be updated accordingly.	The company has provided a response to B1 with reasonable and appropriate justification for choice of comparator. Please see below for a re-iteration of the response to clarification question B1: *"In patients with vitiligo whose disease has not responded to initial treatment with TCS or TCI, the current BAD guidelines recommend offering either NB-UVB +/- TCS or TCI, or considering oral betamethasone specifically for rapidly progressive disease[1]. Neither of these options are appropriate comparators for the appraisal of ruxolitinib cream for the following reasons:* *A retrospective cohort study amongst vitiligo patients in the UK found that among the prevalent cohort of 44,910 patients in 2019, 85.0% of patients were not on vitiligo-related treatment. In the first year after diagnosis, 60.8% of patients did not receive any vitiligo-related treatment (e.g., topical*	The EAG does not consider this to be a factual inaccuracy. The statement in the EAR is correct. No change has been made to the EAR.

		steroids, topical calcineurin inhibitors, oral steroids, phototherapy), increasing to ≥82.0% from the second year onward[2]. This finding is indicative of the vast majority of prevalent patients, including those with prior failure with TCS or TCI, not proceeding to another line of off-label therapy. In the first year, patients were recorded as having been prescribed topical corticosteroids (29.1%), topical calcineurin inhibitors (11.8%), and oral corticosteroids (4.2%). From the second year onward, the percentage of patients prescribed oral corticosteroids remained stable, while prescription of topical corticosteroids and calcineurin inhibitors declined to 11.4% and 3.9% in the second year, respectively, remaining low thereafter[2]. *Given the availability of generic TCS and TCI, ruxolitinib cream is not anticipated to be cost-effective in the full population. Therefore, this positioning is considered most appropriate since introduction of a topical treatment after failure of initial topical treatment but prior to*	

		phototherapy is less burdensome for patients with vitiligo and less of a strain on NHS resources. Furthermore, there remains a lack of equitable access to phototherapy, which is further compounded by other competing chronic inflammatory skin disease indications for phototherapy such as psoriasis and atopic dermatitis, resulting in long wait times and variability in receiving this treatment option across the UK. Finally, and more fundamentally, clinicians generally recommend that phototherapy is prioritised for patients with large BSA (i.e., >10%) affected [3,4]. *Oral betamethasone is not an appropriate comparator as it is explicitly recommended only for rapidly progressive disease[1], whereas the vast majority of patients in TRuE-V1 and TRuE-V2 had stable disease[9-11].”* Specific inaccuracies related to the positioning of ruxolitinib 1.5% cream and the lack of feasibility of an indirect treatment comparison are discussed above.	

The EAG make the following statement on pg 92: *"In a separate part of clarification question B8, the EAG also requested that the company use these data to incorporate functionality into the revised model to allow time-to-treatment discontinuation to be accurately modelled. The company did not do this."*	The company propose that the entire sentence be removed from the report.	As part of the clarification call held on 1st September at 14.00-15.00, it was agreed between the company and the EAG that the incorporation of TTD into the cost-effectiveness model was not required. This agreement was acknowledged by the company as part of the response to clarification question B8: *"At the clarification call with the EAG on the 1st September 2023, it was agreed that the incorporation of time-to-treatment discontinuation (TTD) within the revised model was not required."* The company note the following text on pages 92/93 of the EAG report: *"In light of the ruxolitinib data in **Error! Reference source not found.**, the EAG were not overly concerned by the assumption of time-invariant treatment discontinuation in the analysis, though more accurate use of the available treatment discontinuation data would have been preferred in the first instance."*	The EAG does not consider this to be a factual inaccuracy. This request was made at the clarification stage of the appraisal, and the company did not provide the analysis requested. The EAG does not recall any agreement with the company that could be construed as withdrawing the request made in the clarification question. Nevertheless, the statement in the EAR is correct. No change has been made to the EAR.

The EAG make the following statement on pg 111: *"There was no evidence that the company validated model outcomes against published estimates from external studies or with clinical experts."*	The company propose that the entire sentence be removed from the report.	The model structure, inputs and model outputs were validated with clinical experts and health economic experts with the summaries of the validation meetings having been provided to the EAG as part of the clarification questions (B4)[3,14]. Regarding the validation of outcomes against published estimates, this was not possible as there is no precedent of published cost-effectiveness models in vitiligo. Utility estimates from the mapping algorithm applied in the model were compared against the EQ-5D-based utilities derived from the Hi-Light study[15]; please refer to clarification question B15.	The EAG does not consider this to be a factual inaccuracy. For clarity, the EAR stated that there was no evidence presented regarding validation of model *outcomes* (i.e., not model *inputs*) with either clinical expert opinion or published estimates from external studies. No change has been made to the EAR.

Issue 4 Approach to ruxolitinib dosing assumptions in the cost-effectiveness model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG make the following statement on pg 18: *"The EAG used a mean ruxolitinib dose estimate from TRuE-V summary data provided by the*	Please could the EAG add the following sentence following the paragraphs on pg 18: *"The EAG recognises that using the mean dose may not be*	The company would like to highlight that using the mean or maximum recommended dose to calculate expected ruxolitinib 1.5% cream consumption, as conducted	The EAG does not consider this to be a factual inaccuracy. The EAG does not agree with the company's assessment of

company in response to clarification question B10 to inform dose expectations in its preferred analyses. As this mean estimate was greater than the maximum recommended dose in the product licence for ruxolitinib, the EAG presented two alternative dosing approaches: one in which the cost of mean dose was assumed, another in which the cost of maximum recommended dose was assumed. The difference between these approaches was the difference between EAG-preferred tentative base cases 1 and 2 (Section 6.3)." *"Using the mean TRuE-V ruxolitinib dose (or maximum recommended dose) as a proxy for the expected ruxolitinib dose increased the expected cost of ruxolitinib…"* *On pg 82:* *"The EAG considered the use of vehicle cream dosing data in combination with ruxolitinib dosing data to estimate expected ruxolitinib dosing data to be inappropriate, when ruxolitinib*	*appropriate as it is higher than the maximum recommended dose in the product license."* Pg 82 text to be updated to the following: *"The EAG recognised the use of vehicle cream dosing data in combination with ruxolitinib dosing data to estimate expected ruxolitinib dosing data was a conservative assumption made by the company."*	by the EAG, is inappropriate. The EAG acknowledge that the data are skewed (pg 83), and accordingly should have preferred the median over the mean. Leveraging the maximum use in the trial and SmPC for a patient with 10% BSA, is not aligned with the expected average BSA of patients living with Vitiligo. As stated in response to clarification question B10, in a real-world setting, it is likely that the consumption of ruxolitinib cream would be lower. This is evidenced by the VALIANT study[16], which gives a median affected BSA (% of total body) of 3.78 compared to 7.70 from the TRuE-V studies (pooled TRuE-V; Table 8 presented in Document B). The median BSA population in TRuE-V1/2 studies are higher due to the inclusion criteria of 3.5-10% BSA and higher compliance observed in clinical trial vs real-world. The model assumes a daily dose based on the observed median weight of intervention and vehicle cream (4.03g) applied during the	the relative usefulness of median and mean estimates in the presence of a skewed distribution. The EAG also does not consider the company's preferred approach to dosing assumptions as conservative. No change has been made to the EAR.

dosing data could be used in isolation."		24-week period in the pooled TRuE-V studies [9-11] resulting in a conservative estimation of usage having been applied in the cost-effectiveness analysis. Further, the mean usage employed by the EAG is inconsistent with the marketing authorisation for ruxolitinib 1.5% cream which limits usage to two tubes per month[13]. This is acknowledged by the EAG on page 81: *"The SmPC and Information for patients leaflet each stated that no more than two 100g tubes per month should be used."* Errors made in the dosage calculations conducted by the EAG are presented in 'Errors identified in EAG's revisions to the cost-effectiveness model'.	
The EAG make the following statement on pg 49: *"The Phase II trial of ruxolitinib (see Section 3.2.2) included a dose comparison and showed that increased efficacy is possible with higher doses of ruxolitinib, but the highest dose used in the trial was*	The company would like the following sentence added following the statement on pg 49: *"However, the EAG recognises that there is limited evidence suggesting that increased dose leads to improved efficacy"*	The EAG statement suggests that there is a correlation between amount of ruxolitinib cream used and efficacy. The company would like to emphasize that F-VASI50 and T-VASI50 were similar between 1.5% QD and BID in the Phase 2 trial as given by Figure 2	The EAG does not consider this to be a factual inaccuracy. While full data from the Phase II trial was not presented by the company in the CS, the EAG noted from the publication cited by the company that

the licensed dose and so efficacy evidence is not available for a higher dose"		(efficacy of varying doses of ruxolitinib cream or vehicle cream)[17].	increased efficacy was shown as compared between lower (0.15% and 0.5% once daily) and higher doses (1.5% once or twice daily). The EAG statement in the EAR was that increased efficacy with higher doses is possible, which the EAG considers to be correct. No change has been made to the EAR.

Issue 5 Approach to resource use and cost assumptions in the cost-effectiveness model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG make the following statement on pg 18: *"The EAG was also concerned that the company's psychological support assumptions overestimated the proportion of patients who would receive NHS psychological support."*	The company would like the sentence to be updated to reflect that the psychological support assumptions were based on feedback received from clinicians. That is, "*The EAG was also concerned that the company's psychological support assumptions, based on clinical discussions, overestimated the proportion of patients who would receive NHS psychological support."*	The company detailed in its submission that psychological support was based on a simple average of clinical experts' suggestion, with Appendix M detailing the calculations.	The EAG does not consider this to be a factual inaccuracy. Details of the source of the inputs were referenced where relevant in the EAR. The statement in the EAR represents the view of the EAG.

			No change has been made to the EAR.
The EAG make the following statement on pg 103 and 104: *"The EAG was concerned that the company's approach overestimated disease management costs, in a manner that biased cost-effectiveness results in favour of ruxolitinib."*	The company would like the wording to be updated to reflect that the disease management costs were based on the published HI-Light study. Specifically, *"The EAG noted that, although disease management was based on the HI-Light trial, they were concerned that the company's approach may have overestimated disease management costs."*	The disease management resource use was based on Sach et al., which is an economic evaluation of the HI-Light trial[15], as described in the submission. Further detail was provided as part of clarification question B12 and re-iterated below: *"The cost categories considered in TA681[18] are as follows: dermatologist outpatient consultation (consultant led), dermatologist telephone appointment (consultant led), dermatologist nurse visit, GP consultation, hospitalisation, accident and emergency visit. Of note, hospitalisation was not included in the submitted model as clinical validation stated that vitiligo does not lead to hospitalisation (please refer to the 'summary of clinical validation' provided in the reference pack). Further, psychological support was not referenced in TA681[18] (or*	The EAG does not consider this to be a factual inaccuracy. Details of the source of the inputs were referenced where relevant in the EAR. The statement in the EAR represents the view of the EAG. No change has been made to the EAR.

		Sach et al., 2021)[15] but was discussed by clinicians as forming part of the care package for patients due to the psychological impact of vitiligo on patients. The resource use frequencies for psychological support over a six-month period were provided by the two clinicians and a simple average of their values was estimated and then converted to the cycle-specific length of four weeks. The values provided by the clinicians and the associated calculations are provided in Appendix M. The costing categories in Sach et al., 2021[15] were used to inform the TA681 categories as Sach et al is a relevant and recent vitiligo-based trial whilst the evidence presented in TA681[18] contributed to a positive reimbursement decision. *To generate the values for the resource use for the 'initial', 'maintenance' and 'retreated' health states, the TCS arm of the Sach et al.,*	

		publication[15] was used but converted to a four-week resource use. For dermatologist outpatient consultation (consultant led), resource use 1 and 2 were combined; telephone-based appointment was taken as equivalent to 'unscheduled telephone consultation with dermatologist (resource use 3)'; 'dermatologist nurse visit' is formed of the combination of resource use 4, 5 and 6; 'GP consultation' is taken as equivalent to 'primary care and community' (resource use 7); finally, 'accident and emergency' is taken as half of the resource use listed for 'secondary care' (resource use 8). For the non-response state, the same resource use categories are used to generate the resource use values, however, the combination arm from Sach et al., 2021[15] is used to inform these values. Resource use estimates for stable state were retrieved from the two clinicians due to lack of data	

		from any published source, whereas for the stable retreated state the same estimates with those provided for the stable state were assumed. *The resource use, and corresponding cost, was validated by clinicians; please refer to the 'summary of clinical validation' for further detail.* *Please refer to Appendix M for further detail."*	
The EAG make the following statement on pg 103: *"if a comparison to vehicle cream was only potentially appropriate for end-of-line positioning, no NHS Dermatology appointments would be expected in this "non-response" state."*	The company would like the wording to be amended to reflect that patients who are in the system would continue to require monitoring of their disease state as the condition may become progressive. That is, the company suggest that this sentence be removed from the EAG report.	Discussions with clinical experts held by the company, and provided with the clarification questions (B4), note that patients would continue to receive monitoring for their vitiligo as the disease may become progressive. Specific issues relating to the positioning of ruxolitinib 1.5% cream are noted in Key Issue 1 above.	The EAG does not consider this to be a factual inaccuracy. The EAG's view here related to patients being discharged from dermatology following exhaustion of all treatment options, hence no further dermatology appointments would be anticipated. This is an opinion of the EAG, which may be discussed

			by the committee in due course. No change has been made to the EAR.
The EAG make the following statement on pg 100: *"The EAG noted that the company was therefore effectively applying the cost of suncream twice in the vehicle cream arm of the analysis. In addition, the EAG noted that in practice, ruxolitinib use would limit a person's freedom to apply suncream when wanted, as discussed in Section 0. The company did not account for this in their analysis."*	The company would like the paragraph on pg 100 to be amended to the following: *"The EAG noted that the company costed vehicle cream as sunscream, in line with clinical feedback. In addition, the EAG noted that in practice, ruxolitinib use would limit a person's freedom to apply suncream when wanted, as discussed in Section 0. The company did not account for this in their analysis."* The company request 'Section 0' link to be updated throughout the document.	Suncream forms part of both the concomitant therapy and best supportive care received by vitiligo patients, as described in the submission. The components of concomitant therapy and best supportive care were validated with clinicians (the summary of validation meetings is provided as part of clarification question B5). The cost of suncream is applied to vehicle cream as clinical advice received by the company (and presented to the EAG as part of clarification question B4) suggested that this was the most relevant price to apply for vehicle cream in the cost-effectiveness model. Please note that the price of suncream used as part of concomitant therapy and that for vehicle cream are not the	The EAG have updated "Section 0" references in the EAR. The company assumed a different cost for suncream as proxy for vehicle cream versus as part of concomitant therapy. For clarity on this point, the page 100 fragment cited has been updated to read "*"The EAG noted that the company was therefore effectively applying a cost of suncream twice".* No other changes to this part of the EAR have been made.

		same value (£20.60 versus £9.70).	
The EAG make the following statement on pg 101: *"In the EAG's view, such a source and consideration of an active, effective treatment assumption was inappropriate for a health state that was characterised as a "non-response" state."* *And on pg 102 the following related comment is made:* *"In this instance, assuming that any dermatology outpatient attendances or NB-UVB treatment after ruxolitinib or standard of care treatment (as the company do in the "non-response state") would be inappropriate."*	The company request the paragraph *on page 101 to be amended to the following:* *"In the EAG's view, the components of the non-response state are dependent on the positioning of ruxolitinib 1.5% cream"* The company request the paragraph on pg 102 be updated to: *"In this instance, assuming that any dermatology outpatient attendances or NB-UVB treatment after ruxolitinib or standard of care treatment (as the company do in the "non-response state") would be dependent on the positioning of ruxolitinib 1.5% cream."*	The company disagree with the description provided by the EAG regarding the VALIANT study as a source for NB-UVB usage in the non-response state. VALIANT is a cross-sectional study of vitiligo, considered to be reflective of clinical practice, with adult patients diagnosed with vitiligo by a healthcare professional recruited using a general population sampling approach from a network of consumers in multiple countries around the world, including the UK.[6] Further, given the company's positioning as a step-change between first and second line, and based on clinical feedback received by the company (as detailed in response to clarification question B5), the inclusion of dermatology appointments and NB-UVB in the non-response state is appropriate. This aligns with clinical	The EAG does not consider this to be a matter of factual inaccuracy. The cited text represents the EAG's view. No change has been made to the EAR.

		feedback in that patients who do not respond to ruxolitinib 1.5% cream would try other available treatment options, including NB-UVB[3]. Please refer to comments on Key Issue 1 in this document for further justification.	
On pg 101, the EAG make the following statement: *"Clinical advice to the EAG noted that hand-held NB-UVB devices were not available at every NHS center; the average NHS cost of a course of NB-UVB may be greater than £775 as a result, but the EAG expected that £16,478.36 was a marked overestimation."*	The company request the statement on pg 101 to be updated to the following: *"Clinical advice to the EAG noted that hand-held NB-UVB devices were not available at every NHS centre; the average NHS cost of a course of NB-UVB may be greater than £775 as a result."*	As noted in the company's submission, the company's 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[19]. The frequency and time period of phototherapy use was validated with clinicians[3]. The company notes that the EAG acknowledge issues around access to handheld NB-UVB devices resulting in a higher cost for NB-UVB than they suggest i.e., £775.	The EAG does not consider this to be a factual inaccuracy. The statement in the EAR represents the EAG's view. No change has been made to the EAR.

		Please refer to comments on Key Issue 1 in this document for further justification.	

Issue 6 Approach to patient utility assumptions in the cost-effectiveness model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG make the following statement on pg 19: *"It was not clear that the company used their systematic review to identify the best available data to inform utility assumptions but given the TRuE-V HRQoL data collected and issues with indirect comparisons cited in the CS, there may not be substantial additional published data to further resolve uncertainty"*	The company propose the following wording: *"The company provided full detail of the systematic review conducted to identify HRQoL data as part of its submission; it is unlikely that there is any substantial additional published data to further resolve uncertainty. However, the EAG notes that the technical report embedded within Appendix O details comparisons between vitiligo-specific mapping algorithms and other identified mapping algorithms, which may help reduce uncertainty".*	The company provided the details of the systematic literature review conducted to identify HRQoL data as part of Appendix H. Appendix H thoroughly presents the detail of the review. Further, as noted by the EAG on page 94, the company provided *"(i) the appropriate section of the CS, (ii) Appendix O of the CS, (iii) a technical report embedded within Appendix O of the CS, (iv) Appendix I of the technical report embedded within Appendix O of the CS, and (v) protocols and Excel files containing regression analysis results embedded within Appendix I of this technical report"*, thus emphasizing the breadth of data provided to the EAG to showcase the company's evidence review and generation. The company notes that none of the published	The EAG does not consider this to be a factual inaccuracy. Reporting a systematic search and review is not the same as demonstrating that that review has been used to identify the best available data to inform cost-effectiveness analysis assumptions. No change has been made to the EAR.

		DLQI data were specific to vitiligo patients. Notably, Table 1 & Table 2 of the technical report included in Appendix O make comparisons between vitiligo-specific mapping algorithms and other mapping algorithms which were identified which could aid in reducing the uncertainty.	
The EAG make the following statement on pg 97 and 115: *"As illustrated by EAG clarification question B15, the expected utility values assumed for "Maintenance period", "Stable" and "Stable retreated" health states were higher than the age-equivalent general population utility value from a source commonly cited in NICE appraisals[37]. Notably, this same source was used in the company's own model to adjust utility for the effect of ageing over the model's time horizon."*	The company would like it to be acknowledged that they disagree with the EAG's argument that the utility estimates lack face validity.	The company would like to reiterate its response provided as part of clarification questions B15: *"Where a general population utility estimate of 0.903 is observed for a 38-year-old, it is not uncommon for utility values reported in RCT data to be higher than the expected population estimate. For example, if we consider the HI-Light trial, a pragmatic UK RCT where EQ-5D data was collected for patients with Vitiligo, EQ-5D utility values of 0.9287 and 0.9182 were reported for patients 9 months post treatment (Sach et al., 2021, Supplementary Table 3)[15].* *In addition to this, uncertainty around mean predicted utility values for the UK general*	The EAG does not consider this to be a factual inaccuracy. The statement in the EAR represents the EAG's view. No change has been made to the EAR.

		population are not reported in the cited source (Ara and Brazier, 2010[20]). Therefore, the plausible range of estimates with a degree of confidence (e.g., using 95% confidence or credible intervals) is unknown, in particular the plausible upper bounds. *In a separate publication (Janssen et al., 2021)[21], population utility estimates across 5 European countries including the UK, taking into account age and gender are reported along with estimates of variability, allowing for calculation of confidence intervals for the plausible range of values for utility estimates. An estimate of a Standard Deviation (SD) of around 0.171 (Table 3 of the reference) is reported. When this value of uncertainty is applied to the utility estimate of 0.903 for a 38-year-old, the 95% confidence interval (95% CI) is [0.893, 0.913]. When considering the entire European population, the population mean for someone aged 38 is expected to be around 0.939 (Table 3 of the reference)[21]. The 95% CI for this value, assuming the same SD of 0.171 is [0.929, 0.949]. This upper*	

		limit includes the values of 0.935 and 0.945 and are considered plausible estimates in a European population. This is consistent with the expected benefits of ruxolitinib cream across European populations. *The burden of disease is reflected in the utility estimates. Intuitively, it is observed that non-responders have the lowest EQ-5D utility value: patients classified as 'non-responders' have smaller treatment benefit compared to those who respond (F-VASI50/75/90 responders). The observed increasing trend in utility as treatment response increases is consistent with improvements in HRQoL measures also reported in this submission. The observed improvements from ruxolitinib cream underline the burden relief in this patient population. Details of the burden of disease are further highlighted in detail in Section B.1.3.1.2 of the submission.* *There is no apparent reason why utilities should not decrease post baseline, particularly for patients*	

		not benefiting from treatment (i.e., non responders). Published studies do report utility decrements over time (e.g., Grandy et al. 2012)[22]. *One plausible explanation as to why post baseline utilities are lower than baseline utilities for the non-responder group at week 24 (in the prior therapy sub-population as well as the overall population) is that the decrease (in post baseline utilities) is driven largely by the higher proportion of non-responders who were in the vehicle group. Around 82% of non-responders were in the placebo arm and 50% of non-responders were in the ruxolitinib cream treatment arm. It would therefore not be unexpected that vehicle non-responders have a deteriorating vitiligo condition over and above ruxolitinib cream non-responders. This is further reflected by the mean utilities for vehicle vs ruxolitinib cream as observed in Table 1 of the document supporting the response to this clarification question (please refer to the document titled 'Data to support the response of*	

		EAG clarification B15'). Mean reductions in change from baseline to week 24 utilities (mean CFB) also show differences between treatment groups for non-responders, with vehicle patients reporting larger mean CFB differences. This is further corroborated when considering other vitiligo or dermatology specific measures such as the VitiQoL and DLQI: 23% of vehicle patients reported increased (worsening) VitiQoL total scores at week 24 in the non-responder group compared to 15% on ruxolitinib cream (in the non-responder group). Similar trends were observed with DLQI (total score) at week 24 (worsening score). *When considering non responders overall (ignoring treatment), patients with de-pigmentation (worsening of skin condition) reported poorer HRQoL in other measures (see Table 2 of the document supporting the response to this clarification question). As the mapping model implemented is based on percentage pigmentation values, patients with*	

		depigmentation will drive the utility value down, and this is also reflected in outcomes such as VitiQoL, DLQI and VNS scores (Table 2). For patients with depigmentation vs repigmentation: there were higher (worse) mean DLQI scores: 4.05 vs 3.74 and higher (i.e., worse HRQoL) mean VitiQoL scores: 39.23 vs 34.80. Patients who experienced depigmentation at week 24 also reported worse VNS outcomes: 22.5% vs 55% noted their vitiligo was 'less noticeable' or 'no longer noticeable' for de-pigmentation vs re-pigmentation (Table 2). Consequently, there appears to be strong alignment between HRQoL, clinical outcomes and mapped EQ-5D utilities."	
The EAG make the following statement on pg 94: *"Instead, the company used an opaque and loosely justified approach to derive health state utility values that involved using F-VASI results from TRuE-V1 and TRuE-V2 in combination with a*	The company would like the following update to the text on pg 94: *"The company used a published mapping algorithm and various assumptions to derive health state utility values that involved using F-VASI results from TRuE-V1 and TRuE-V2 studies".*	The company, as noted by the EAG, provided an extensive amount of detail regarding the utility analysis: *"(i) the appropriate section of the CS, (ii) Appendix O of the CS, (iii) a technical report embedded within Appendix O of the CS, (iv) Appendix I of the technical report embedded within Appendix O of the CS, and (v)*	The EAG does not consider this to be a factual inaccuracy. The statement in the EAR represents the EAG's view. No change has been made to the EAR.

published mapping algorithm and various assumptions." *And on pg 97:* *"The quality of reporting by the company with respect to the approach and justification for each choice and assumption required to reach the utility values in* ***Error! Reference source not found.*** *was a barrier to review and further reduced confidence in the appropriateness of the values selected."*	The company requests the removal of the text on page 97.	*protocols and Excel files containing regression analysis results embedded within Appendix I of this technical report".* As such, it is not reasonable to argue that the approach is opaque and loosely justified or that the quality of reporting is a barrier to review.	

Issue 7 Approach to adverse event assumptions in the cost-effectiveness model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On pages 20, 98-99 and 104 the EAG raise concerns with the modelling of adverse events in relation to HRQoL and cost impacts with the following specific comments made:	The company would like the wording as noted in the first column to be updated to accurately account for the responses provided by the company. Specifically, the following changes are requested: *Pg 20*	The company accounted for the impact of adverse events in line with clinical advice and previous submissions in dermatology (TA534 and TA681)[18,23], as detailed in the submission documents.	The EAG does not consider this to be a factual inaccuracy. The wording used in the EAR is correct. No change has been made to the EAR.

Pg 20 *"In response, the company did not comply with the EAG's request, or alter their CS approach to account for adverse events in the cost-effectiveness analysis in any way."* *Pg 99* *"the company declined to do so, without reasonable justification"* *Pg 104* *"In EAG clarification question B16, the EAG asked the company to extend the scope of adverse events included in the cost calculation, to capture treatment-emergent adverse events occurring in ≥ 1% of patients in any treatment group. In reply, the company declined to amend their original approach."* The company take objection to the EAG's language including: • *'did not comply with..'* • *'declined to do so without reasonable justification'*	*"In response, the company did not comply with the EAG's request, or alter their CS approach to account for adverse events in the cost-effectiveness analysis in any way."* *To* *"In response, the company re-iterated its position regarding the modelling of adverse events in the cost-effectiveness analysis."* *Pg 99* *"the company declined to do so, without reasonable justification."* *To* *"the company provided reasonable justification as to its approach."* *Pg 104* *"In EAG clarification question B16, the EAG asked the company to extend the scope of adverse events included in the cost calculation, to capture treatment-emergent adverse events occurring in ≥ 1% of patients in*	In response to clarification question B16, the company provided reasonable justification for not having included the HRQoL impacts of adverse events. The response was as follows: *"Thank you for the suggestion. The model includes treatment-emergent adverse events (TEAEs) that occurred in ≥4% of patients in any group in the 24-week period corresponding to the double-blind period of the TRuE-V studies. In line with previous NICE submissions in dermatology (TA534 and TA681)[18,23], only the cost impact of adverse events are considered in the model. This is also in line with the clinical validation conducted by the company (please refer to the summary of clinical validation provided as part of the responses to the clarification questions), which highlights that patients do not experience a detrimental impact to their quality of life. Thus, only the cost impact of adverse events impacting ≥4% of patients is captured. This enables the capture of relevant and realistic impacts that would be expected to*	

• *'declined to amend their original approach'*	*any treatment group. In reply, the company declined to amend their original approach."* To "*In EAG clarification question B16, the EAG asked the company to extend the scope of adverse events included in the cost calculation, to capture treatment-emergent adverse events occurring in ≥ 1% of patients in any treatment group. In reply, the company re-iterated its position."*	*be experienced by patients and are likely of generating a cost impact on the NHS. The use of ≥ 1% would potentially lead to the capture of costs which would not be borne by the NHS."* The company also note the following (contradictory) statement made by the EAG: *"Ruxolitinib was associated with a small increase in the risk of adverse events compared to vehicle cream. Mostly these were mild adverse events but there was an increased risk of adverse events affecting the treated area, including acne, pruritus, erythema and rash. The EAG considered that these would not contribute to major health concerns or healthcare resource use, though considered that people using ruxolitinib who experience these events may be more likely to discontinue treatment or else change the application of ruxolitinib to another area of the body."* In conclusion, the company approach to incorporation of adverse events in the model is	

		reasonable, as agreed by the EAG in the above sentence. The company addresses the 4% cut-off in the following row.	
The EAG make the following statement on pg 104: *"Firstly, 4% is an arbitrary and high cut-off, while 1% is an established cut-off for "common" adverse events, as noted in European Medicines Agency documentation[24]. Secondly, if this appriasal led to a positive recommendation for ruxolitinib at the end of the existing treatment line, it will replace no treatment, and thus definitively introduce toxicity"*	The company request the EAG to remove this sentence.	The company notes that the EAG references the European Medicines Agency (EMA); the company does not consider this appropriate as the EMA is a regulatory agency. The MHRA has assessed the safety of ruxolitinib 1.5% cream and has granted ruxolitinib 1.5% cream a marketing authorisation. This confirms the safety of the intervention, thus the comment by the EAG that ruxolitinib cream would thus '*definitively introduce toxicity*' is inaccurate. The company would like to refer the EAG to the safety data presented within the submission and available in the EPAR[9]. Of note, neither the MHRA nor the EMA assigned a Black Triangle for ruxolitinib 1.5% cream. The company addresses points made regarding the positioning of ruxolitinib cream in Key Issue 1.	The EAG does not consider this to be a factual inaccuracy. The statement in the EAR is correct, in that ruxolitinib would definitively introduce toxicity as compared to no treatment. The typo in the quoted statement had been amended (p.104).

		The 4% cut-off was used to select the five most common treatment-emergent adverse events in the economic model, similar to the approach considered in TA681[18]. As such, the cut-off was not arbitrary.	

The company have identified errors in the EAG's revisions to the cost-effectiveness model which are noted in the following table.

Errors identified in EAG's revisions to the cost-effectiveness model

Description of error	Specifics around the error	Requested updates to the model	EAG response
Weighted average for no response utilities calculations. Calculations tab cell L122.	The EAG have estimated the no response utilities as a weighted average between the utilities for non-responders and the utilities for FVASI50-74 to reflect the response threshold used. However, the number of patients ([redacted]) who achieved FVASI50-74 is incorrect as it includes patients who achieved FVASI75 and FVASI90. The correct number is [redacted] and therefore the weights used for estimating no response utilities should be updated accordingly.	The cost-effectiveness model shared by the EAG should be revised to account for this error in the no response utilities and the results should be updated accordingly. In the tentative base case scenario 2, this results in a decrease of the ICER to £47,257/QALY when applying treatment-specific weights in each arm.	Thank you for raising the [redacted] versus [redacted] issue. The EAG has addressed this in the post-FAC version of the EAR and related materials. Specifically, the relevant cell range containing the value [redacted] was replaced with the value [redacted]. The other values included in this breakdown of patient numbers by response category were also edited for the same reasons (but do not have an impact on the EAG's

	In addition, the company believes that the weights should be specific to ruxolitinib cream and vehicle cream, respectively, to accurately reflect the proportion of patients who achieved FVASI50-74, thus no response utilities should also be specific to each arm in the model. That is, a weight of [redacted] should be assigned to ruxolitinib cream and a weight of [redacted] should be assigned to vehicle cream for F-VASI50-74.		preferred utility value for the 'no response' health state). Regarding the company's second point, the EAG does not consider arm-specific utility values to be appropriate for the 'no response' health state. In brief, this is because the 'no response' utility value is used over the course of the model time horizon, and any differences in the average utility for patients in this health state according to prior treatment are not expected to continue indefinitely.
Sustained response assessment at week 52. Intervention and comparator trace tabs, cell Y34.	The EAG have altered the timing of initial response assessment one cycle earlier (i.e., from week 24-28 to week 20-24), however, the same was not done for the sustained response assessment occurring at week 52. For consistency, week 52 assessment should also have been updated to be one cycle earlier.	The cost-effectiveness model shared by the EAG should be revised to account for this inconsistency in the timing of assessing sustained response and the results should be updated accordingly.	Thank you for raising this. The EAG agrees with the company's requested update to the model, and this has been addressed in the post-FAC version of the EAR and related materials. To address this error, the cell range on the patient flow sheets containing the value 52 was replaced with the value 48 (i.e., 52 – 4). Text in Section 6.1 of the EAR has

			also been updated to describe this edit.
The EAG state on page 82 that a dosage of 6.57g per day for ruxolitinib cream could be used as patients may in practice have in mind the stated limit of two tubes a month. The EAG then proceed to apply a dosage of 7.14g per day in their scenario analysis.	The company note that the EAG have divided 200g (two tubes of 100g each) by 28 days (to give 7.14g) as opposed to 30.44 days, which is the correct number of days per month (applied in EAG tentative base case scenario 2).	The maximum dosage should be 6.57g per day to accurately reflect the average number of days per month.	Thank you for raising this. As the SmPC wording is "*No more than two tubes of 100 grams a month*", the EAG agrees that the maximum advised dose should in the base case be interpreted as 200g every 30.4375 days (365.25 days / 12 months) and has amended the EAR and related materials accordingly. Nevertheless, the EAG highlights three points relevant to the use of 28 days: 1. 28-day prescribing is recognised as a means of reducing drug wastage and accounting for patient convenience (see, for example, local prescribing guidance for NHS West Essex [link], NHS Lancashire Medicines Management Group

			[link], and NHS Nottingham and Nottinghamshire [link]) 2. The TRuE-V study protocols note that *"Participants will be instructed to document treated areas and advised to limit use to no more than one 60 g tube per week"*. This equates to a maximum of 240 g per 28 days, or 260.89 g per 30.44 days 3. The company chose to use a 28-day model cycle length; it is this interval that determines when costs are assumed to be applied Taking these points into consideration, the EAG considers it plausible that some patients may receive two tubes of ruxolitinib cream every 28 days and therefore

			include a scenario to this effect in the updated EAR.

(please cut and paste further tables as necessary)

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