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

Slides for public – contains no confidential information

Technology appraisal committee D [11 January 2024]

Chair: Megan John

Lead team: Matt Bradley, Carole Pitkeathley, Ben Searle

External assessment group (EAG): Peninsula Technology Assessment Group (PenTAG)

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Company: Incyte

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

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Summary

NICE National Institute for Health and Care Excellence

Vitiligo

Background

- Vitiligo is a chronic auto-immune condition:
  - immune system attacks melanocytes that produce the skin pigment melanin
  - areas of skin lose normal pigment → become very pale, white or light pink and burn easily in the sun
  - **non-segmental vitiligo (NSV): symmetrical patches can appear on both sides of the body**

Symptoms and prognosis → not life-threatening, but can cause psychological distress

- Vitiligo can affect any area of the skin but commonly affects the face, neck, hands and skin creases
- Thyroid disease and other autoimmune conditions are more common in individuals with vitiligo
- NSV generally progresses slowly and has an unpredictable course

Epidemiology

- In the UK, ~1 in 100 people have vitiligo, of which 85% to 90% have NSV
- In England, ~450,000 people (aged ≥12 years) have NSV, of which around ~45,000 have facial involvement*

Sources: company submission, British Association of Dermatologists vitiligo patient information leaflet, NICE final scope for ID3998, NHSE BIA submission*

Note: slide has been updated after the committee meeting to correct for factual inaccuracies

Summary of patient and clinical perspectives

Submissions from 2 patient experts, Vitiligo Support UK, Vitiligo Society, 2 clinical experts and British Association of Dermatologists (endorsed by Royal College of Physicians)

- Vitiligo is often considered a cosmetic condition but can have a significant social and psychological impact on a person and their quality of life:
  - social rejection, identity loss, stress, humiliation and impact on self-esteem and self-image
  - fear about developing new patches, other autoimmune conditions
  - avoidance of the sun and/or risk sun burns with minimal exposure
- People with vitiligo can feel dismissed by healthcare professionals who may lack specialised knowledge, including psychological support needed
- Unmet need for people with vitiligo → current treatments are not licensed for vitiligo and limited in effectiveness
- Difficult to access treatments due to long NHS dermatology waiting lists:
  - availability of phototherapy varies across hospitals, where available can be inconvenient and costly to access (e.g. time off work, travel)
  - people with vitiligo often self-fund treatments*

*such costs are not specified in the NICE reference case

"This disease changes you physically and psychologically. The way that you saw yourself, the person you were, this disease takes that away from you"

"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..."

See appendix – Patient perspectives and Clinical perspectives

Equality considerations

Potential equality issues raised during scoping and/or in submissions

- Vitiligo is more common in younger people, so [if recommended] making the treatment available for children over 12 years of age is important
- Vitiligo is more noticeable in darker skin tones:
  - psychological impact and risk of sunburn is apparent for all skin tones
  - treatments should be offered to all people irrespective of their skin type, colour and other traits
  - there may be an additional cultural burden in people with darker skin tones which may lead them to experiencing a greater level of discrimination
- Risk of depression and anxiety which may be greatest in Black and minority ethnic populations
- Some vitiligo quality-of-life measures may discriminate against non-native English speakers
- Access to phototherapy for people with vitiligo varies across the country

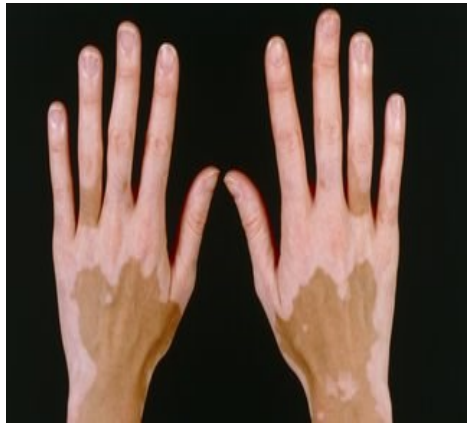

Figure 1: NSV (source NHS health: vitiligo)

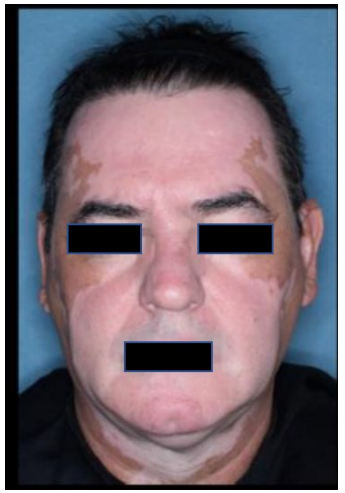

Figure 2: NSV (source company submission)

The committee can only appraise ruxolitinib cream within its marketing authorisation

Are there any equality issues that need to be considered?

Abbreviations: NSV; non-segmental vitiligo

Ruxolitinib cream (Opzelura, Incyte)

See appendix – Ruxolitinib cream

Marketing authorisation (MA)	• Ruxolitinib cream (1.5%) is indicated for the treatment of NSV with facial involvement in adults and adolescents from 12 years of age • MHRA MA issued 4 July 2023 • [redacted]
Mechanism of action	• Janus Kinase inhibitor → reduces destruction of melanocytes by immune system
Administration	• 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)*, with a minimum of 8 hours between 2 applications • No more than 2 tubes of 100 grams a month should be used • Satisfactory repigmentation may require treatment beyond 24 weeks • Treatment can be stopped once satisfactory repigmentation is achieved (no need to taper therapy) and reinitiated if depigmentation recurs after stopping treatment
Price	• The company has a confidential commercial arrangement [simple discount patient access scheme (PAS)]

*10% BSA represents an area as large as 10 times the palm of one hand with the 5 fingers

Abbreviations: MHRA, Medicines and Healthcare products Regulatory Agency; NSV, non-segmental vitiligo

Treatment pathway

No previous NICE technology appraisals for vitiligo, current treatments are used off-label

Based on British Association of Dermatologists guidelines for the management of vitiligo (2021)

1st line

- Topical corticosteroid* or topical tacrolimus (facial vitiligo or photo-exposed areas for non-facial vitiligo)

2nd line

- Phototherapy (NB-UVB → whole body or localised) +/- topical corticosteroid or calcineurin inhibitors (such as tacrolimus)
- Oral betamethasone + phototherapy for rapidly progressive disease

3rd line

- Excimer laser/light + topical calcineurin inhibitors
- Cellular grafting
- CO_2 laser + 5-fluorouracil cream
- Depigmentation (bleaching) therapies

Treatments not widely available on NHS

Supportive measures

- Vitamin D supplement
- Cosmetic skin camouflage
- UVA SPF 50 sunscreen
- Psychological support

- Company considers that ruxolitinib will be prescribed in secondary care
- Company UK cohort study (n=44,910 in 2019) suggested that 85% of people were not on active vitiligo treatment
- EAG clinical expert: ~20-30% with NSV have rapidly progressive disease

Stakeholders → many people with vitiligo do not receive active therapy:

- Long dermatology waiting lists
- Difficulties accessing phototherapy (long waiting lists, competing with other skin diseases that require shorter courses, personal time constraints and associated cost)
- Unsuitability or contraindication to existing 2nd line therapies

*can be given in alternation with topical tacrolimus for areas with thinner skin

Abbreviations: NB-UVB, narrow-band ultraviolet B therapy; NSV, non-segmental vitiligo; UVA SPF, ultraviolet A sun protection factor

Key issues

Issue	ICER impact
Positioning of ruxolitinib cream and comparators • Is the comparator no active treatment or phototherapy? Or both? • Is no active treatment a comparator only if person has had all active treatments? • Would ruxolitinib cream be used in people with rapidly progressive disease?	**Unknown, likely large**
Clinical data for prior therapy subgroup • Generalisability of overall population to the proposed 2nd line population for ruxolitinib cream? Should company provide more analyses?	**Unknown**
Model structure and use of clinical data • Is the modelled continuation criterion valid? Does the model have face validity?	**Unknown, likely large**
Dosing assumptions • How will dosing be managed in clinical practice? What is the best way to estimate the costs of ruxolitinib cream?	**Large**
Resource use and cost assumptions • What proportion of people on BSC have phototherapy and how many dermatology visits would they have? What proportion of people have psychological support?	**Large**
Utility values • Which approach (company or EAG) is appropriate? Is QoL captured in model?	**Moderate**
Adverse event assumptions • What is the impact of any AE with ruxolitinib cream on discontinuation, QoL?	**Unknown**

Abbreviations: AE, adverse event; BSC, best supportive care; QoL, quality of life

Unknown impact, likely large

Positioning of ruxolitinib cream and comparators

Background

See appendix – Decision problem (comparators)

- Company's positioning: people ≥12 years with non-segmental vitiligo (NSV) with facial involvement which has not responded to topical corticosteroids or topical calcineurin inhibitors, or for whom these treatments are unsuitable → narrower than marketing authorisation (which would allow 1st line use)
- Company consider there is a place in the treatment pathway after topical 1st line treatments and before phototherapy where people have no treatment → company comparator is no active treatment (vehicle cream)

1st line

- **Topical corticosteroid or topical tacrolimus (facial vitiligo or photo-exposed areas for non-facial vitiligo)**

2nd line

- **Phototherapy (whole body or localised) +/- topical corticosteroid or calcineurin inhibitors (such as tacrolimus)**
- **Oral betamethasone + phototherapy for rapidly progressive disease**

3rd line

No active treatments routinely used in NHS

Company proposed: ruxolitinib cream [ID3998]

EAG → phototherapy (+/- topical treatments) should be comparator for ruxolitinib used after topical treatments. No evidence for this comparison presented by company

EAG comments

- Agree many people may not receive active treatment for vitiligo, but still need to determine the clinical and cost effectiveness of ruxolitinib cream compared to existing 2nd line treatments used in the NHS
- No active treatment is a potential comparator if ruxolitinib used after phototherapy (at 3rd line)

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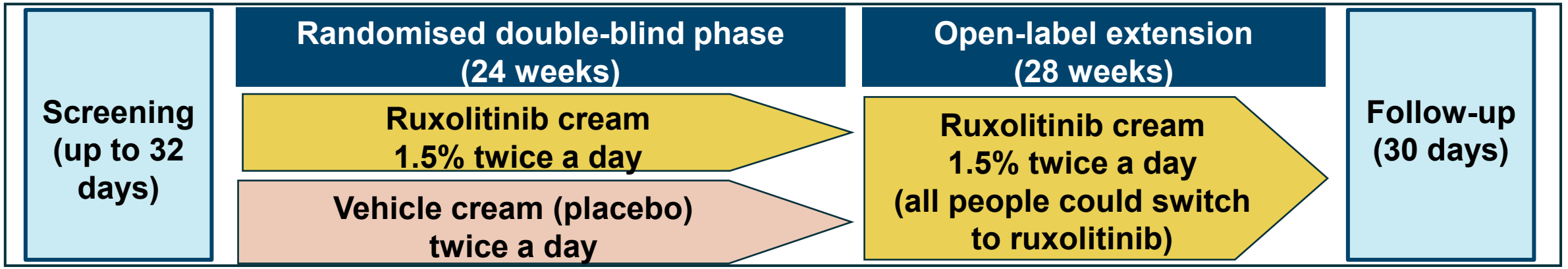
Key clinical trials – TRuE-V1 and TRuE-V2

See appendix – Clinical section

	TRuE-V1 and TRuE-V2 studies (identical design - company pooled data)
Population: **TRuE-V1, n=330** **TRuE-V2, n=344**	People aged ≥12 years with non-segmental vitiligo: • ≥ 0.5% BSA on the face and ≥ 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 • international trials (no UK sites)
Dosing	Ruxolitinib or vehicle cream applied twice daily (up to 10% BSA), max 1 x 60g tube/week
Previous treatments	Topical corticosteroids, topical calcineurin inhibitors, vitamin D derivatives, phototherapy and other treatments
Primary outcome	Proportion achieving F-VASI75 (≥75% improvement from baseline) at week 24



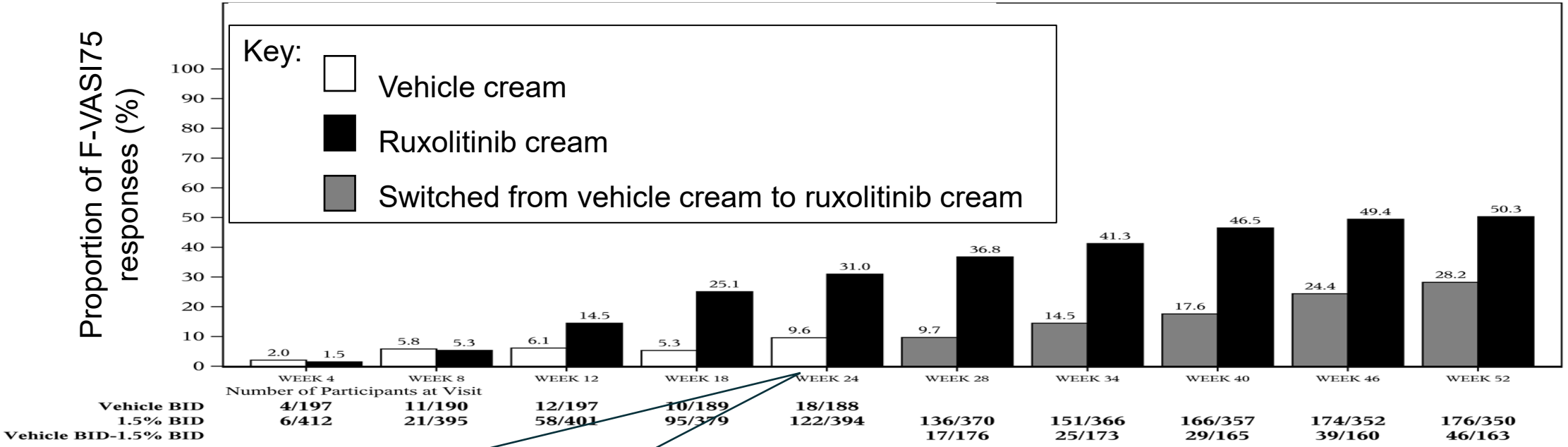
Clinical advice to the EAG is that VASI assessments of vitiligo are a highly accurate measure but are typically not used in clinical practice due to the time needed to perform the assessment

Abbreviations: BSA, body surface area; F-VASI, facial Vitiligo Area Scoring Index; T-VASI, total body Vitiligo Area Scoring Index

Note: slide has been updated after the committee meeting to correct for factual inaccuracies

TRuE-V1 and TRuE-V2 pooled results

Proportion achieving F-VASI75 from week 4 to week 52 (ITT population)



Week 24	Primary outcome	
	Vehicle cream (n=218)	Ruxolitinib cream (n=443)
Response rate (standard error)	9.6% (2.17)	30.7% (2.29)
Odds ratio	4.17 (95% CI 2.43, 7.14), p-value <0.0001	

Open label extension, increased response rate over 52 weeks

See appendix – Subgroup analyses

Abbreviations: CI, confidence interval; F-VASI, facial Vitiligo Area Scoring Index, ITT; intention-to-treat

Unknown impact

Key issue: Clinical data for prior therapy subgroup

Background

- Clinical evidence is not consistent with target population or population used in the model (see table below)

Populations (pooled TRuE-V1 and TRuE-V2)	Full trial population	Prior therapy subgroup (used in model = any previous treatment)	Prior therapy subgroup (target population = after topical 1st line treatments, before phototherapy)
Clinical evidence presented by company	✓	Limited – see EAG critique below	X

EAG comments

- Clinical effectiveness evidence presented in the company submission is based on the pooled full trial populations, only 28% of whom had previously received topical corticosteroids or calcineurin inhibitors
  - unclear how generalisable the full trial population is to the proposed 2nd line population for ruxolitinib
- Company's evidence for prior therapy subgroup (used in model) could not be appraised by EAG:
  - EAG noted a slightly higher response rate to ruxolitinib in those who had previously received treatment compared to the full trial population → absence of complete population characteristics/outcome data means it is unclear if this is evidence of a true difference in treatment effect between treatment lines
  - comprehensive submission of evidence for subgroup needed to validate suitability for use in model

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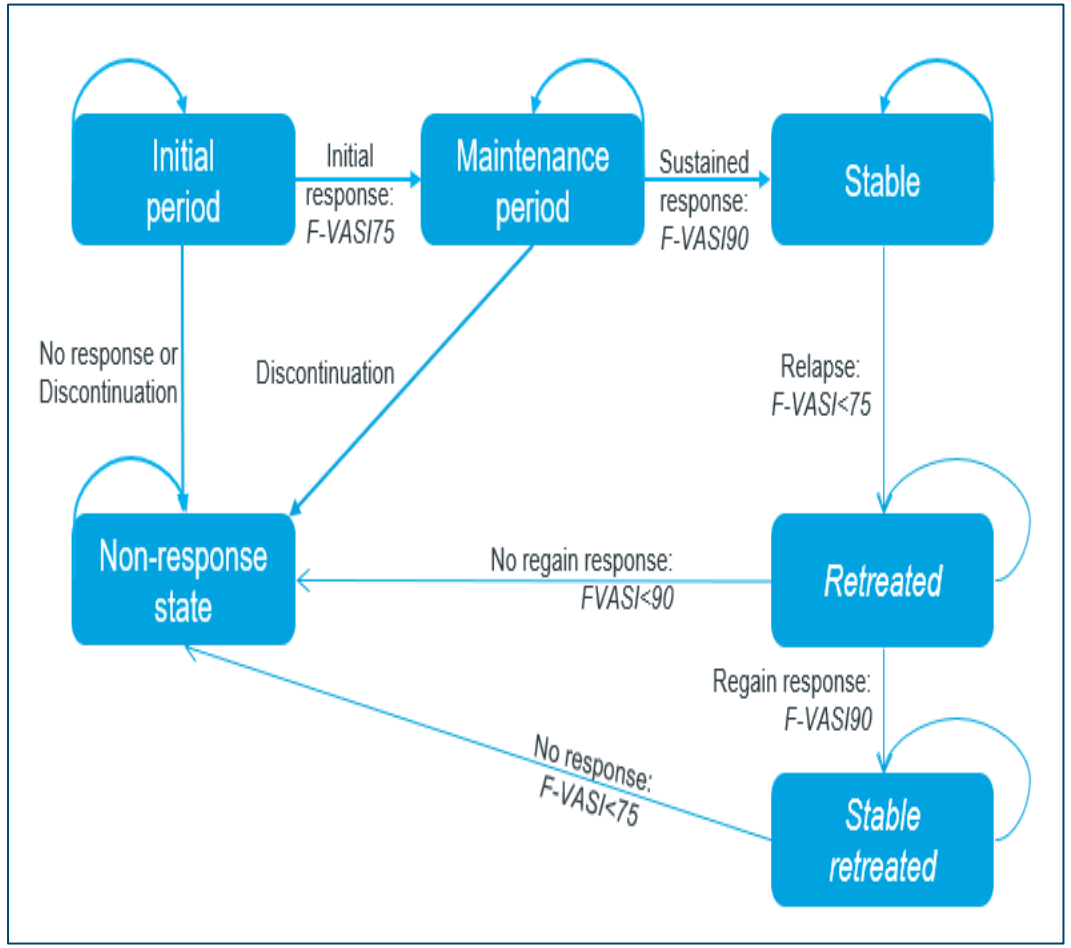
Company's model overview



*BSC = phototherapy (NB-UVB), vitamin D supplement, camouflage, fixing powder and sunscreen

Markov state-transition model

- Model population had received "prior therapy"
- 7 mutually exclusive health states: death not presented in figure, but reachable from all other health states
- All patients enter the initial period and receive either ruxolitinib or vehicle cream (no alternative active therapy in 2nd line)
- Maintenance period health state split into 2 states with different utility values:
  - F-VASI 75-89 or F-VASI ≥90
- Stable state = patients receive no treatment
- Retreatment occurs once only with either ruxolitinib cream or vehicle cream (no further retreatment occurs)
- All people in the non-response state receive BSC*
- Costs in non-response state discontinue after 10 years
- Cycle length: 4-weeks with half-cycle correction
- Time horizon: lifetime (64 years)

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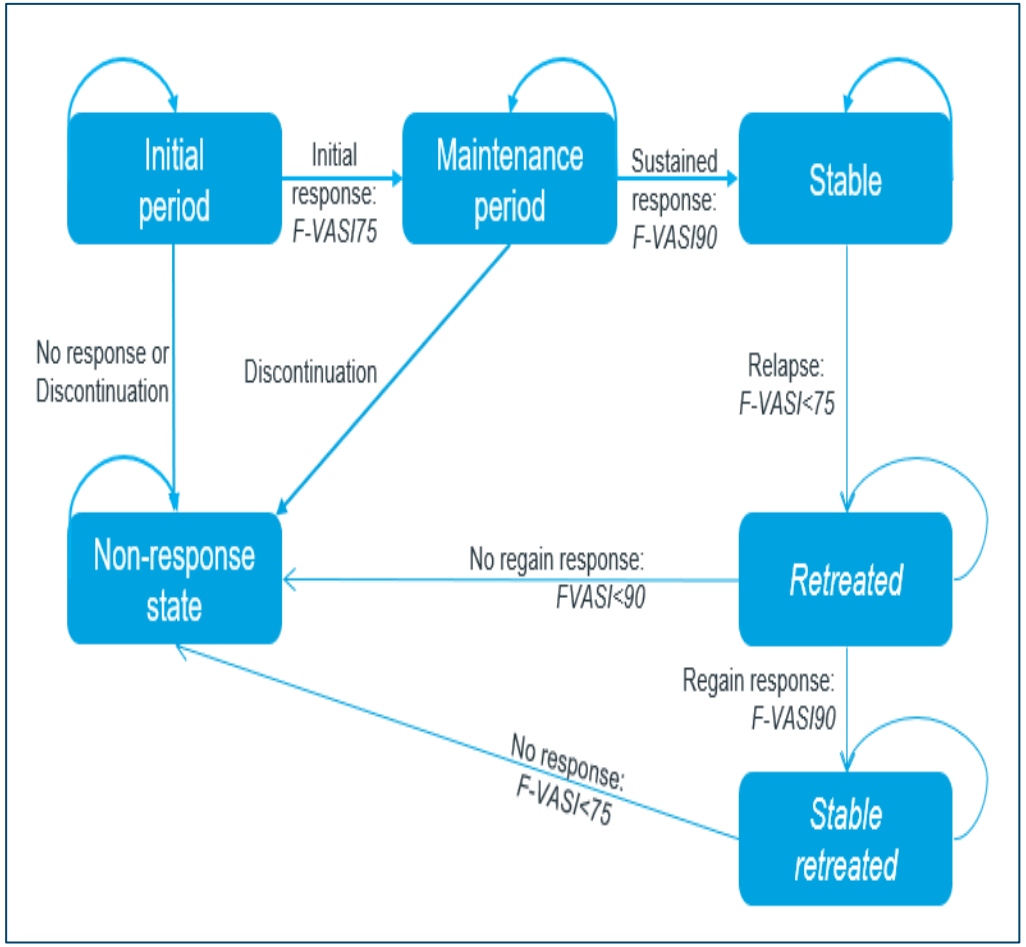
Abbreviations: BSC, best supportive care; F-VASI, facial Vitiligo Area Scoring Index; NB-UVB, narrow-band ultraviolet B therapy

Unknown impact, likely large

Key issue: Model structure and use of clinical data



See appendix – Model structure and use of clinical data

Abbreviations: F-VASI, facial Vitiligo Area Scoring Index

EAG comments on company model

- Comparison to vehicle cream is only relevant as an end-of-line treatment not 2nd line
- Little confidence in model because of implausible assumptions/structural issues:
  - Model assumes patients with a F-VASI 50-74 at 24 weeks are non-responders & stop treatment – not aligned with expected NHS clinical practice nor company trials. May underestimate costs and benefits of ruxolitinib
  - Non-responders receive active treatment, a significant proportion receiving phototherapy, but not able to improve and continue to accrue costs for 10 years
  - Patients in maintenance with a F-VASI 75-89 cannot improve further and cannot advance to stable state
  - Relapse leads to retreatment with the same prior treatment. Re-treatment with vehicle cream does not reflect NHS practice
- Only costs for adverse events (AEs) that occurred in ≥4% of patients included. Disutility due to AEs not included

Large impact

Key issue: Dosing assumptions

See appendix – Dosing assumptions

Background

- Company base case assumes that the pooled median daily dose of treatment in TRuE-V trials (ruxolitinib cream or vehicle cream) reflects the expected daily dose of ruxolitinib cream in NHS practice

EAG comments

- Dose is likely to vary for each person and will depend on adherence to SmPC
- It is more appropriate to use the mean dose of ruxolitinib, rather than the median dose across arms
- EAG noted that the mean dose of ruxolitinib in the pooled trials was larger than both the median and the dose limit of ruxolitinib as specified in the SmPC
  - Implying, some people in TRuE-V studies used more ruxolitinib than is recommended in the SmPC

	TRuE-V trials	SmPC	Company base case	EAG tentative base cases
Ruxolitinib dosing	**Max 240g/28 days** (1 x 60g tube/week)	**Max 200g/month** (2 x 100g tubes/month)	Median TRuE-V trials*: **113g/28 days** (modelled as 4.03g/day)	1) Mean TRuE-V trials**: **213g/28 days** (modelled as 7.61g/day) 2) Max dose of ruxolitinib in SmPC: **200g/month** (modelled as 6.57g/day)

*week 1 to 24

**week 1 to 52, ruxolitinib arm only

Abbreviations: SmPC, summary of product characteristics

Note: slide has been updated after the committee meeting to correct for factual inaccuracies

Large impact

Key issue: Resource use and cost assumptions (1)

Treatment in non-response state

- People on vehicle cream progress more quickly to non-response state and therefore spend longer incurring costs over model time horizon
- Non-response state in model includes phototherapy costs (as part of BSC), every 4-week cycle
- Company assume [redacted]% of people in non-response state receive hospital-based phototherapy
  - these people are assumed to have a 9-month course of hospital-based phototherapy every year

EAG comments

- If company's proposed positioning is appropriate, expected cost of hospital-based phototherapy in non-response state is overestimated → biases cost-effectiveness results in favour of ruxolitinib:
  - proportion in non-response health state who receive phototherapy is overestimated
  - company state that home–based phototherapy (which is cheaper) would be suggested for facial vitiligo
  - given NHS dermatology capacity constraints near continuous phototherapy is not plausible
- EAG believe comparison with vehicle cream is only appropriate as an end-of-line treatment:
  - in this case, assuming phototherapy treatment after ruxolitinib or standard of care would be inappropriate → EAG removed phototherapy costs in non-response health state

Abbreviations: BSC; best supportive care

Large impact

Key issue: Resource use and cost assumptions (2)

Disease management

Assumption	Company base case	EAG base case
Proportion of patients receiving psychological support (number of appointments assumed for an average patient in each health state within a given month)	Initial, maintenance periods and retreated: 0.690 Stable disease and stable retreated states: 0.230 Non-response state: 1.380	0.15 (15% - for all health states based on clinical advice)
NHS dermatology appointments in non-response health state	Included (~every 2 months for 10 years post baseline)	Removed (assuming ruxolitinib cream is positioned at end-of-line)

EAG comments

- Company's approach overestimates disease management costs and does not align with current NHS dermatology resource constraints → biases cost-effectiveness results in favour of ruxolitinib cream

Moderate impact

Key issue: Utility values

Background - EQ-5D data were not collected in TRuE-V1 and TRuE-V2 trials

- Company calculated EQ-5D-3L values from F-VASI scores collected in the TRuE-V trials
- This required an assumption that F-VASI is proxy for the repigmentation score (RPS) allowing the application of an algorithm developed by Begum et al. (2023)
- Both F-VASI and RPS are measures of change in pigmentation from baseline → so baseline utility estimates were derived by applying baseline VitiQoL scores to the mapping algorithm (**EAG note different approach underlying initial period health state to other health states)**
- Regression analyses were performed to estimate change in utility from baseline to 24 weeks
- EAG has several concerns with this approach and the validity of the utility values generated

EAG notes that for F-VASI 50-74 the company approach generates a utility of 0.890, but in the model these patients are non-responders and assigned a value of 0.797 → EAG preferred to apply weighted average of no-response and F-VASI 50-74 values (See appendix – Utility values)

Health state	Utility values applied in company base case
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

EAG notes that these bold values are higher than age-equivalent general population → lack face validity

Abbreviations: EQ-5D, EuroQol 5-dimension; F-VASI, facial Vitiligo Area Scoring Index; VitiQoL: vitiligo-specific quality-of-life instrument

Unknown impact

Key issue: Adverse event assumptions

Background

- Company's analysis does not include HRQoL implications of adverse events (AEs)
- Treatment-arm specific AE costs were included for those occurring in ≥4% of people in either arm (up to week 24) across TRuE-V1 and TRuE-V2
- Treatment-related AEs affected 47.7% of ruxolitinib participants in the pooled TRuE-V population

EAG comments

- Though ruxolitinib is a topical treatment with no clear safety concerns in registrational trials, EAG is concerned that the company is introducing bias in favour of ruxolitinib:
  - 4% is an arbitrary and high cut-off
  - If ruxolitinib is considered at end-of-line, it would replace no treatment and so AEs would be a burden
  - TRuE-V data showed that some people may have used more ruxolitinib than indicated in the product licence → this may result in safety issues unanticipated with intended use
- Given the magnitude of incremental QALY gains for ruxolitinib cream, it is plausible that accounting for the HRQoL implications of AEs appropriately could meaningfully affect cost-effectiveness results
- EAG asked the company at clarification to incorporate utility and cost implications for adverse event data (occurring in ≥1% of people in any treatment group) into its analyses, but company declined to do so

Abbreviations: HRQoL, health-related quality of life; QALY, quality-adjusted life year

Company base case results – prior therapy subgroup

ICERs include PAS discount for ruxolitinib cream

Deterministic base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Vehicle cream	[redacted]	[redacted]	[redacted]	[redacted]	13,634
Ruxolitinib cream	[redacted]	[redacted]			

Probabilistic base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Vehicle cream	[redacted]	[redacted]	[redacted]	[redacted]	14,676
Ruxolitinib cream	[redacted]	[redacted]			

Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year

Differences between company and EAG preferred assumptions

	Company base case	EAG tentative base case
Minor EAG amendments	Not included	Included
Treatment pathway + associated costs	• Ruxolitinib used after topical treatments compared to vehicle cream, before phototherapy / 2nd line therapies • Dermatology visits ~every 2 months for 10 years in non-response state • Amount of psychological support dependant on health state (slide 19)	• Ruxolitinib used at end-of-line versus no active treatment: ○ No vehicle cream or phototherapy costs ○ No dermatology visits in non-response state ○ All health states receive the same level of psychological support per month
Utility values	• Utility values estimated through manipulation of trial data. Values generated for some health states above those of general population. • Non-response utility: 0.797	• Utility values capped at general population in response states • Non-response utility set to a weighted average derived from no response (0.797) and F-VASI 50-74 values (0.890)
Ruxolitinib dosing	Median from TRuE-V studies	Base case 1: Mean from TRuE-V studies Base case 2: Max SmPC dose
Duration of costs in non-response state	10 years	Lifetime
Missing data (no regain of response transition)	Average of 1) removing missing data and 2) assume as non-response data (slide 54)	Assume as non-response data

EAG concerns with model structure could not be addressed in its exploratory base case analyses

Abbreviations: F-VASI, facial Vitiligo Area Scoring Index; SmPC, summary of product characteristics

EAG tentative base case results – prior therapy subgroup

Deterministic results (unless otherwise stated) - ICERs include PAS discount for ruxolitinib cream
EAG assumptions on treatment pathway + costs and ruxolitinib dosing have greatest impact on ICER

Scenario/EAG revisions (R) (Ruxolitinib cream versus vehicle cream)	Incremental results		ICER
	Costs (£)	QALYs	£/QALY
Company base case	[redacted]	[redacted]	**13,634**
R1) Minor EAG amendments	[redacted]	[redacted]	13,031
R2) Treatment pathway + associated costs	[redacted]	[redacted]	100,036
R3) Utility values	[redacted]	[redacted]	22,639
R4) Ruxolitinib dosing: mean dose (TRuE-V studies)	[redacted]	[redacted]	97,359
R5) Ruxolitinib dosing: maximum recommended dose	[redacted]	[redacted]	73,000
R6) Duration of non-response costs	[redacted]	[redacted]	4,114
R7) Missing data	[redacted]	[redacted]	16,283
EAG tentative base case 1 (R1-R4, R6-R7)	[redacted]	[redacted]	**303,189**
EAG probabilistic tentative base case 1	[redacted]	[redacted]	**329,105**
EAG tentative base case 2 (R1-R3, R5-R7)	[redacted]	[redacted]	**262,880**
EAG probabilistic tentative base case 2	[redacted]	[redacted]	**283,278**

EAG only presented tentative base case results given concerns raised in key issues regarding model integrity

Abbreviations: ICER, incremental cost-effectiveness ratio; PAS; patient access scheme; QALY, quality-adjusted life year

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Key issues

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Clinical data for prior therapy subgroup • Generalisability of overall population to the proposed 2nd line population for ruxolitinib cream? Should company provide more analyses?	**Unknown**
Model structure and use of clinical data • Is the modelled continuation criterion valid? Does the model have face validity?	**Unknown, likely large**
Dosing assumptions • How will dosing be managed in clinical practice? What is the best way to estimate the costs of ruxolitinib cream?	**Large**
Resource use and cost assumptions • What proportion of people on BSC have phototherapy and how many dermatology visits would they have? What proportion of people have psychological support?	**Large**
Utility values • Which approach (company or EAG) is appropriate? Is QoL captured in model?	**Moderate**
Adverse event assumptions • What is the impact of any AE with ruxolitinib cream on discontinuation, QoL?	**Unknown**

Abbreviations: AE, adverse event; BSC, best supportive care; QoL, quality of life

Thank you.

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Supplementary appendix

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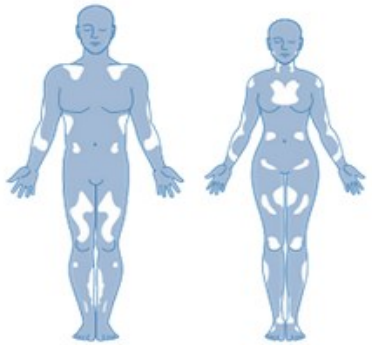
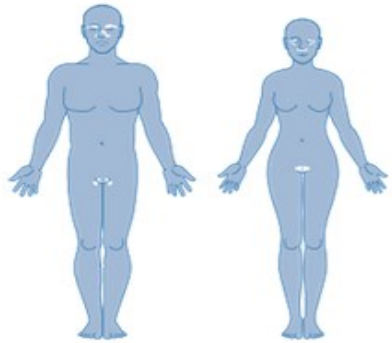
Non-segmental vitiligo (NSV) classification

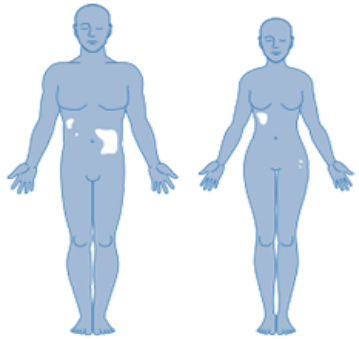
Generalised and acrofacial vitiligo are the most common forms of NSV



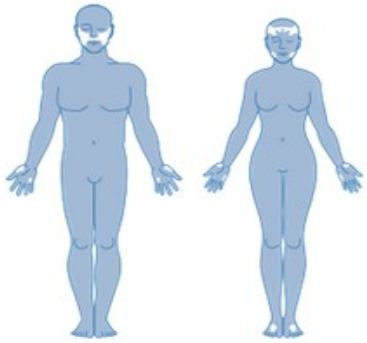
Generalised/common - affects any part of the skin, mainly hands, fingers, face, and trauma-exposed areas



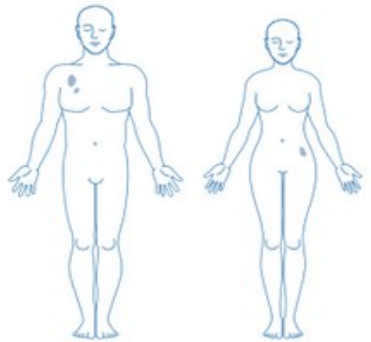
Mucosal - affects the genital and oral mucosae



Focal - Small and isolated lesions with no obvious pattern which do not usually evolve for long periods



Acrofacial - affects the face, head, hands, and feet and typically involves the perioral region and the extremities of digits



Universal - affects the largest extent of the skin (80–90% of the body surface) and usually occurs in adulthood

Source: adapted from company submission

Assessment of disease extent (1)

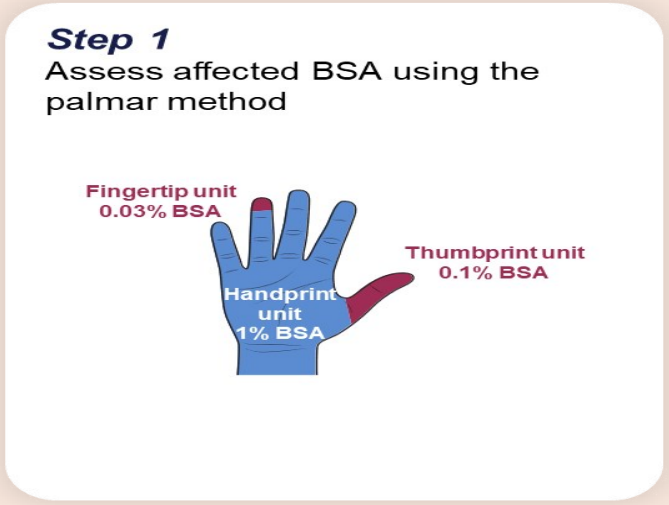
Company note that there is no consensus on the methods to assess the extent of a person's vitiligo
Body surface area (BSA) and Vitiligo Area Scoring Index (VASI) are used in key clinical trials

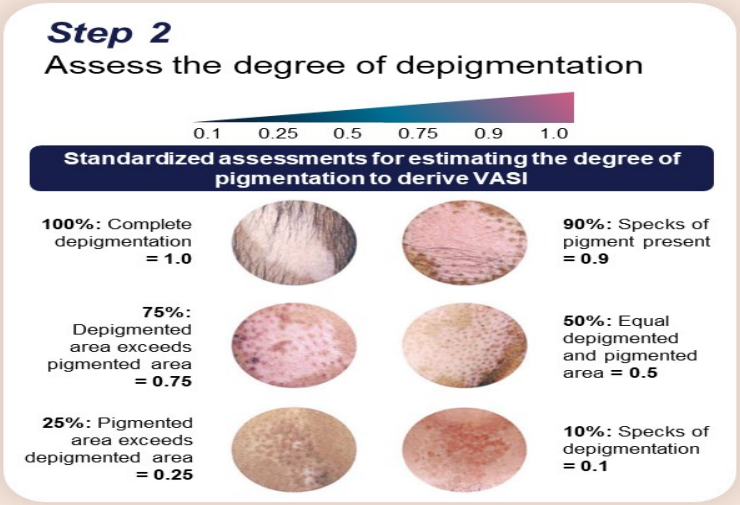
BSA

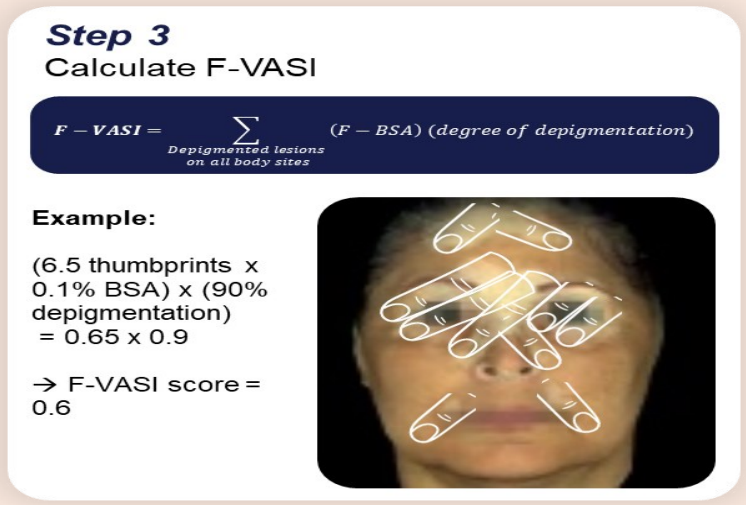
- Palmar method used to assess skin disease extent as a percent of total BSA assuming:
  - Handprint as 1% BSA (palm + 5 digits, with fingers tucked together & thumb tucked to the side)
  - Thumbprint as 0.1% BSA

Facial vitiligo (measured using F-VASI)

- Calculated by multiplying F-BSA (affected areas on the face as a percentage of the total body area, measured using the palmar method) by the degree of depigmentation
- Scores range 0 to 3, with higher scores indicating a greater area of facial depigmentation







Source: company submission

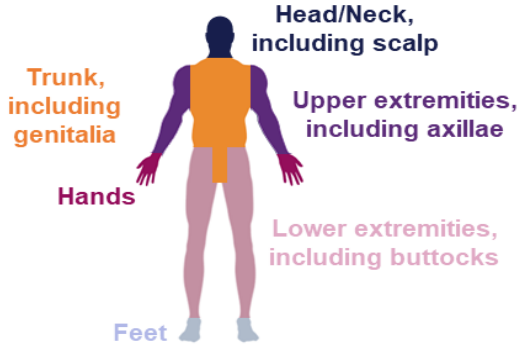
Assessment of disease extent (2)

Total body vitiligo (measured using T-VASI)

- Calculated by multiplying T-BSA (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)

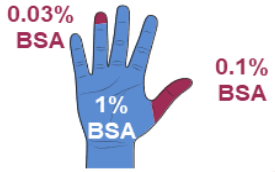
Step 1

Segment the body in 6 anatomic regions



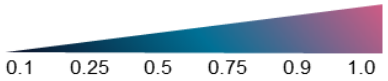
Step 2

Assess affected BSA using the palmar method

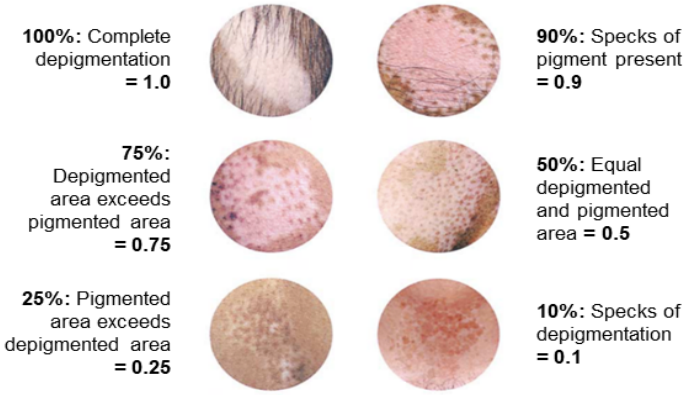


Step 3

Assess degree of depigmentation



Standardized assessments for estimating the degree of pigmentation to derive VASI



Step 4

Multiply the T-BSA by the degree of depigmentation for each body region

Add the product of all body regions

Location	T-BSA	Degree of depigmentation	VASI score per region
Head/Neck, including scalp	Max: 9.0	0.1/0.25/0.5/0.75 /0.9/1.0	
Upper extremities, including axillae (excludes hands)	Max: 14		
Hands	Max: 4		
Trunk, including genitalia (excludes buttocks)	Max: 33		
Lower extremities, including buttocks (excludes feet)	Max: 36		
Feet	Max: 4		
TOTAL			T-VASI score

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

EAG comments

- Clinical advice to the EAG is that VASI assessments of vitiligo are a highly accurate measure but are typically not used in clinical practice due to the time needed to perform the assessment

Source: company submission. Abbreviations: BSA; body surface area; VASI; Vitiligo Area Scoring Index

Patient perspectives

Submissions from 2 patient experts, Vitiligo Support UK and Vitiligo Society

- Vitiligo is often considered a cosmetic condition but can have a significant social and psychological impact on a person and their quality of life:
  - social rejection, identity loss, stress, humiliation and impact on self-esteem and self-image
  - fear about developing new patches, other autoimmune conditions
- People with vitiligo can feel dismissed by healthcare professionals who may lack specialised knowledge, including psychological support needed
- Unmet need for people with vitiligo:
  - current treatments are unlicensed and limited in effectiveness with high risk of vitiligo returning and side effects with long-term use
  - phototherapy can be inconvenient and costly to access (e.g. time off work, travel)
  - people often self-fund treatments* (e.g. phototherapy devices)
- Ruxolitinib cream brings hope to people with vitiligo to live a 'normal' life by potentially restoring the pigment in their skin

*such costs are not specified in the NICE reference case

"This disease changes you physically and psychologically. The way that you saw yourself, the person you were, this disease takes that away from you"

"As a person of colour, I have to live with this every day …Looking so different to other members of your family is awful too, it robs you of your identity completely."

"….the uncertainty of how my skin will look in months and years to come has been hard to manage as new patches appear…it's the vitiligo on the visible areas of my body that I find hardest to cope with."

Link to Patient and clinical perspectives

Clinical perspectives

Submissions from 2 clinical experts and British Association of Dermatologists (endorsed by Royal College of Physicians)

- Vitiligo is a highly visible, debilitating and psychologically devastating skin condition, which usually appears in young people and results in:
  - avoidance of the sun and/or risk sun burns with minimal exposure
- Urgent unmet need for people with vitiligo:
  - no licensed treatments for vitiligo available on the NHS, outcomes often unsatisfactory with current treatments
- Long waiting lists for NHS dermatology secondary care (~12-24 months)
- Many people are unable to start phototherapy in secondary care because of:
  - time constraints → attend hospital 2-3 times/week for up to 12 months
  - long waiting lists → not available in all dermatology clinics and other skin conditions which require shorter courses are often prioritised
- Ruxolitinib cream is likely to be less burdensome than phototherapy (in terms of number of hospital appointments needed)

"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..."

"It is anticipated that ruxolitinib cream will achieve more successful repigmentation resulting in decrease in clinical encounters and improvement in quality of life…"

Ruxolitinib cream (Opzelura, Incyte)

Administration	Summary of product characteristics (SmPC) states that: • People should avoid washing treated skin for at least 2 hours after application of ruxolitinib cream • Other topical medicines (including sunscreen or emollients) used to treat other conditions on the same skin areas should be applied with a minimum of 2 hours after applying ruxolitinib cream

EAG comments

- In the TRuE-V trials, sunscreen, emollients and camouflage were required to be removed from the skin prior to applying ruxolitinib cream
- EAG considered that these restrictions were sensible but may be challenging to adhere to in clinical practice and so may reduce the effectiveness of ruxolitinib
- 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

Link to Ruxolitinib cream

Decision problem (population)

Final scope	Company considerations
People aged 12 years and older with NSV with facial involvement	**Narrower than scope and MA**: • People aged 12 years and older with NSV with facial involvement for whom the disease has not responded to topical corticosteroids or topical calcineurin inhibitors, or for whom such treatments are contraindicated, not tolerated or otherwise medically inadvisable

EAG comments

- Clinical effectiveness evidence presented by the company is consistent with population in scope:
  - however, economic analysis is based on a sub-population who have previously received treatment (based on company's positioning of ruxolitinib cream)
- MA limits use of ruxolitinib cream → to be applied to less than 10% BSA:
  - EAG expect that people with a higher overall BSA affected may still be eligible to apply ruxolitinib to some of their vitiligo patches up to this BSA
- EAG noted that those with rapidly progressive disease are not precluded from receiving ruxolitinib

Abbreviations: BSA, body surface area; MA; marketing authorisation; NSV, non-segmental vitiligo

Decision problem (intervention)

Final scope	Company considerations
Ruxolitinib cream	As per scope

EAG comments

- In the TRuE-V trials, ruxolitinib could be used alongside inactive management strategies (camouflage make-up, sunscreen and emollients) but no active treatments for vitiligo were permitted
- EAG clinical expert considered that they would not prescribe ruxolitinib cream with other active treatments, due to the lack of evidence for the safety of this approach
- SmPC advises against using ruxolitinib cream with other topical medicines used to treat vitiligo on the same skin areas
    - EAG considers that some clinicians may prescribe ruxolitinib cream with other topical treatments used on separate body areas

Abbreviations: SmPC; summary of product characteristics

Decision problem (comparators) (1)

Final scope	Company considerations

Established clinical management without ruxolitinib cream	**Vehicle cream (no active treatment) is the most appropriate comparator:**
	• Availability of generic topical treatments used in 1st line means that ruxolitinib is not anticipated to be cost-effective for use as a 1st line treatment for this population
	• No other treatment currently positioned between 1st and 2nd line in the pathway
	• Existing 2nd line treatments are not appropriate comparators because:
	  ○ most people are not usually receiving active vitiligo-related treatment
	  ○ access to phototherapy is variable and prioritised if large BSA affected (>10%)
	  ○ most people had stable disease [rather than rapidly progressive disease] in key TRuE-V trials (so oral betamethasone is not an appropriate comparator)

EAG comments (1)

- Company submission is based on a comparison between ruxolitinib cream and vehicle cream (no treatment)
- EAG do not disagree with company's proposed positioning of ruxolitinib cream at 2nd line but consider that:
  - the relevant comparators would be existing 2nd line treatments that ruxolitinib would displace (clinical advice to the EAG is that after first-line treatment, a dermatologist would try another treatment option)
  - evidence base submitted by company is not appropriate for decision-making at this position
  - comparison with no treatment is only relevant for the end of the treatment pathway (at 3rd line)

Link to Positioning of ruxolitinib and comparators

Abbreviations: BSA, body surface area

Decision problem (comparators) (2)

EAG comments (2)

- Agree that many people may not receive active treatment for vitiligo, but still need to determine the clinical and cost effectiveness of ruxolitinib cream relative to existing treatments used in the NHS
- Company has not presented sufficient evidence to determine whether people who are not receiving active treatment would do so following the availability of ruxolitinib as a 2nd line treatment
- Clinical advice to the EAG is that people with a BSA <10% may still receive phototherapy
- EAG understood that those with rapidly progressive disease would not be ineligible for treatment with ruxolitinib, and so oral betamethasone may also be a relevant comparator at 2nd line

Stakeholder comments

- Ruxolitinib cream would fit into the 1st line treatment category alongside topical corticosteroids and topical calcineurin inhibitors and possibly following a short trial of these treatments

Link to Positioning of ruxolitinib and comparators

Abbreviations: BSA, body surface area

Decision problem (outcomes)

Final scope	Company considerations
• 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	• Stabilisation of vitiligo was not captured in the TRuE-V studies • Time to relapse (<F-VASI75) in TRuE-V LTE study captures the maintenance of response to treatment

EAG comments

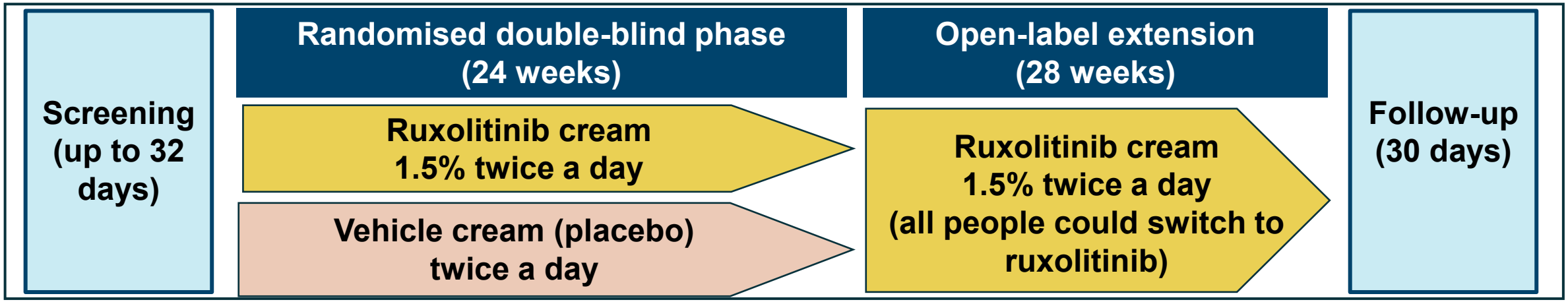
- Agree that evidence for cessation of spread and stabilisation of vitiligo is based on the assessment of relapse rates in the TRuE-V-LTE trial

Abbreviations: F-VASI; facial Vitiligo Area Scoring Index; LTE; long-term extension

Key clinical trials – TRuE-V1 and TRuE-V2

Link to Clinical effectiveness

	TRuE-V1 and TRuE-V2 studies (confirmatory studies supporting the indication)
Design	Phase 3, double-blind, randomised controlled trials (identical design – see figure below)
Locations	45 (TRuE-V1) and 49 (TRuE-V2) centres in North America and Europe (no UK centres)
Population: **TRuE-V1, n=330** **TRuE-V2, n=344**	People aged ≥12 years with non-segmental vitiligo: • ≥ 0.5% BSA on the face and ≥ 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



- Participants were stratified according to geographic region and Fitzpatrick skin type
- Data from all participants at 1 study site (n=13) in TRuE-V2 were excluded due to non-compliance with the study protocol and concerns with data quality
- Permitted concomitant treatments → vitamin D supplements, camouflage, fixing powder and sunscreen

Abbreviations: BSA, body surface area; F-VASI, facial Vitiligo Area Scoring Index; T-VASI, total body Vitiligo Area Scoring Index

TRuE-V1 and TRuE-V2 outcomes

Link to Clinical effectiveness

	TRuE-V1 and TRuE-V2 outcomes
Primary outcome	**Proportion achieving F-VASI75 response:** Decrease (improvement) of at least 75% from baseline in the F-VASI at week 24

Key secondary outcomes	• **Repigmentation (at week 24 and 52):**
	  ○ Proportion achieving F-VASI50, F-VASI75 (week 52), F-VASI90 response (at least 50%, 75%, 90% improvement in F-VASI from baseline, respectively)
	  ○ Proportion achieving T-VASI50, T-VASI75, T-VASI90 response (at least 50%, 75%, 90% improvement in T-VASI from baseline, respectively)
	  ○ Percentage change from baseline in F-BSA score
	• **Cosmetic acceptability (at week 24 and 52):**
	  ○ Proportion achieving a vitiligo noticeability scale (VNS) score of 4 (a lot less noticeable) or 5 (no longer noticeable)
	• **Health-related quality of life**
	• **Adverse effects of treatment**

Stakeholder comments→ repigmentation by at least 75% or a vitiligo noticeability score of 4 or 5 is a clinically significant treatment response

Company used multiple imputation approach to account for missing data in analyses of primary and key secondary outcomes

Abbreviations: F-BSA, facial body surface area; F-VASI, facial Vitiligo Area Scoring Index; T-VASI, total body Vitiligo Area Scoring Index

TRuE-V1 and TRuE-V2 pooled results – secondary outcomes (1)

F-VASI50, F-VASI90, F-BSA at weeks 24 and 52 - ITT population

Week 24	Response rate				% Least squares mean change	
	F-VASI50		F-VASI90		F-BSA	
	Vehicle cream (n=218)	Ruxolitinib (n=443)	Vehicle cream (n=218)	Ruxolitinib (n=443)	Vehicle cream (n=218)	Ruxolitinib (n=443)
	19.6% (SE 2.89)	51.7% (SE 2.46)	1.9% (SE 1.01)	16.0% (SE 1.83)	-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)		14.2% (95% CI 10.1, 18.3)		-20.0% (95% CI -26.2, -13.8)	
Odds ratio	4.40 (95% CI 2.92, 6.65)		10.33 (95% CI 3.31, 32.2)		Not applicable	

Week 52	F-VASI50		F-VASI90		F-BSA	
	Vehicle cream to ruxolitinib (n=163)	Remain on ruxolitinib (n=350)	Vehicle cream to ruxolitinib (n=163)	Remain on ruxolitinib (n=350)	Vehicle cream to ruxolitinib (n=163)	Remain on ruxolitinib (n=350)
Response rate	52.8%	74.6%	14.1%	30.3%	-26%	-42.5%

Data for F-BSA was approximate based on figure curves and error bars and therefore may be inaccurate

Abbreviations: CI, confidence interval; F-BSA, facial body surface area; F-VASI, facial Vitiligo Area Scoring Index; ITT, intention-to-treat; SE, standard error

TRuE-V1 and TRuE-V2 pooled results – secondary outcomes (2)

T-VASI outcomes at weeks 24 and 52 – ITT population

Week 24	T-VASI50		T-VASI75		T-VASI90	
	Vehicle cream (n=218)	Ruxolitinib cream (n=443)	Vehicle cream (n=218)	Ruxolitinib cream (n=443)	Vehicle cream (n=218)	Ruxolitinib cream (n=443)
Response rate (standard error)	5.8% (1.64)	21.9% (2.04)	1.8%	6.1%	0%	0.68%
Difference between arms	16.1 (95% CI 10.9, 21.2)		Not reported		Not reported	
Odds ratio	4.55 (95% CI 2.42, 8.58) p value < 0.0001		Not reported		Not reported	

Week 52	T-VASI50		T-VASI75		T-VASI90	
	Vehicle cream to ruxolitinib (n=163)	Remain on ruxolitinib (n=350)	Vehicle cream to ruxolitinib (n=218)	Remain on ruxolitinib (n=443)	Vehicle cream to ruxolitinib (n=218)	Remain on ruxolitinib (n=443)
Response rate	27.0%	51.1%	7.3%	36.4%	1.8%	4.5%

Treatment effect of ruxolitinib cream for total vitiligo was less than that of facial vitiligo, with fewer participants showing a response in T-VASI

Week 52 data for T-VASI75 and T-VASI90 was only available as a % from the ITT population using the company's multiple imputation analysis

Abbreviations: CI, confidence interval; ITT, intention-to-treat; T-VASI, total body Vitiligo Area Scoring Index

TRuE-V1 and TRuE-V2 pooled results – secondary outcomes (3)

Vitiligo noticeably scale (VNS) score at weeks 24 and 52 – ITT population

Week 24	Vehicle cream (n=218)	Ruxolitinib cream (n=443)
VNS score of 4 or 5 (standard error)	4.2% (1.45)	22.5% (2.09)
Difference between arms	18.3% (95% CI 13.3, 23.2)	
Odds ratio	6.52 (95% CI 3.11, 13.67), p value < 0.0001	

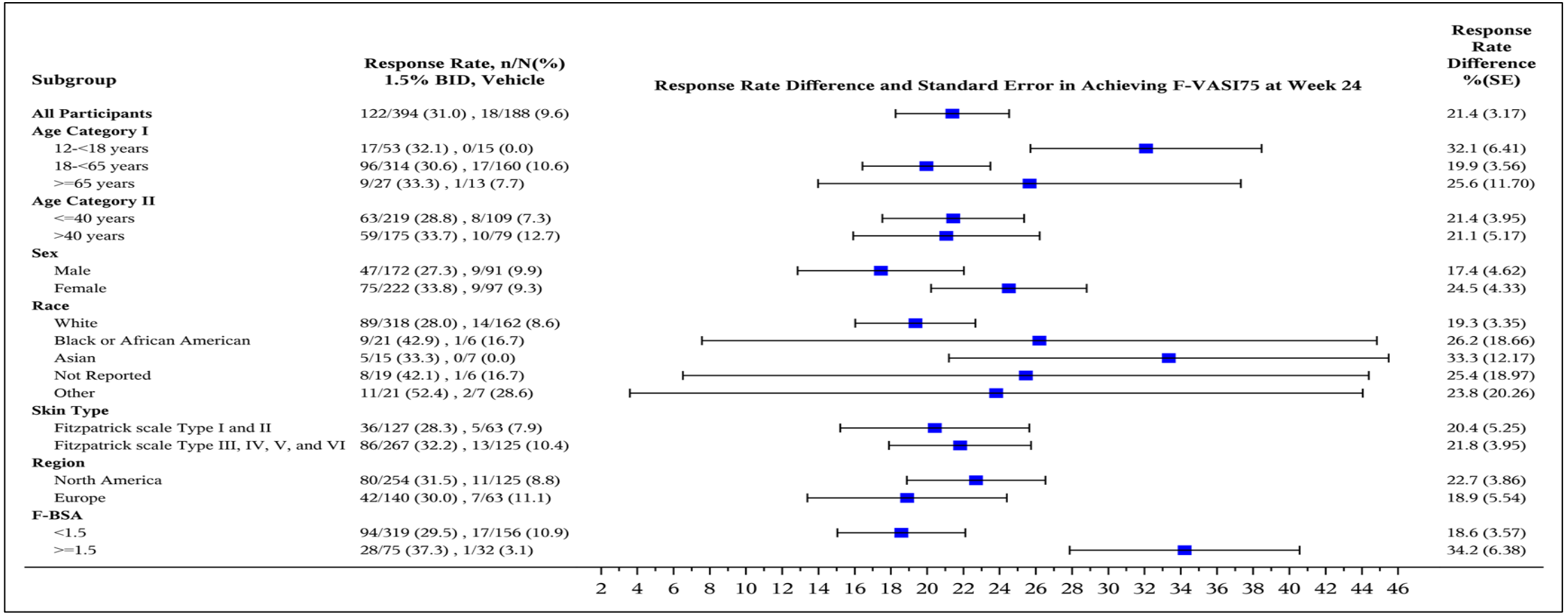
Week 52	Vehicle cream to ruxolitinib cream (n=163)	Remain on ruxolitinib cream (n=350)
VNS score of 4 or 5	16.6%	36.3%

A score of 4 or 5 indicates that a person's vitiligo is no longer noticeable or a lot less noticeable

Abbreviations: CI, confidence interval; ITT, intention-to-treat

TRuE-V1 and TRuE-V2 pooled results – subgroup analyses

Response rate difference in proportion achieving F-VASI75 at week 24 – ITT population



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)

Link to TRuE-V1 and TRuE-V2 pooled results

Abbreviations: F-VASI, facial Vitiligo Area Scoring Index; ITT, intention-to-treat; SE, standard error

TRuE-V1 and TRuE-V2 pooled prior therapy subgroup

Background

- 61% of people from pooled TRuE-V1 and TRuE-V2 received prior therapy for vitiligo
- Company presented additional clinical evidence for prior therapy subgroup in response to clarification, but full population characteristics and outcome data were not provided
- Prior therapy subgroup (any previous treatment, n=411) used in company base case analysis

F-VASI75 at week 24 based on prior therapy (ITT population)

Subgroup	Vehicle cream	Ruxolitinib cream
All patients, n/N (%)	18/188 (9.6)	122/394 (31)
Difference between arms (SE)	21.4 (3.17)	
Prior vitiligo therapy		
Topical corticosteroids, n/N (%)	4/44 (9.1)	39/120 (32.2)
Difference between arms (SE)	23.4 (6.09)	
Topical calcineurin inhibitors, n/N (%)	4/62 (6.5)	44/136 (32.4)
Difference between arms (SE)	25.9 (5.08)	
Phototherapy, n/N (%)	5/64 (7.8)	43/126 (34.1)
Difference between arms (SE)	26.3 (5.39)	

Abbreviations: F-VASI, facial Vitiligo Area Scoring Index; ITT, intention-to-treat; SE, standard error

TRuE-V long-term extension (LTE)

	TRuE-V LTE (68% of people from TRuE-V1 and TRuE-V2 were included in study)
Design	Phase 3 trial with 2 cohorts: • Cohort A = double-blind, placebo-controlled randomised withdrawal and treatment extension study • Cohort B = open-label, single arm treatment extension study
Population and locations	• People who completed either TRuE-V1 or TRuE-V2 (parent studies) and tolerated ruxolitinib cream without safety concerns and with good compliance for continuation • Study locations include those in TRuE-V1 and TRuE-V2

Intervention and comparators	• Cohort A → those who responded* to ruxolitinib in parent studies were randomised to:
	  ○ ruxolitinib cream 1.5% twice a day (treatment extension, n=58) or
	  ○ vehicle cream twice a day (withdrawal, n=58) → ruxolitinib cream given as rescue treatment for those who relapsed** on vehicle cream
	• Cohort B → those who did not respond* to ruxolitinib in parent studies continued ruxolitinib cream twice a day (n=342)

Duration	52 weeks with 30-day follow-up

* Responders defined as those with ≥F-VASI90, non-responders defined as those with <F-VASI90 (at week 52)
** Relapse defined as <F-VASI75 → ruxolitinib cream given in open-label extension until week 104

Abbreviations: F-VASI, facial Vitiligo Area Scoring Index

TRuE-V LTE results

F-VASI75 for those who responded in the TRuE-V1 and TRuE-V2 trials - ITT population

Week 104	Responders (Cohort A)	
	Switched to vehicle cream (n=56)	Remain on ruxolitinib cream (n=55)
<F-VASI75 (relapse)	16 (28.6%)	8 (14.5%)
Primary outcome: time to relapse (days)	NE (95% CI 238.0, NE)	NE (95% CI NE, NE)
Hazard ratio	0.422 (95% CI 0.18, 0.99)	
EAG: <F-VASI75 (relapse) including those censored for treatment discontinuation	29 (51.8%)	15 (27.3%)
EAG: <F-VASI75 (relapse) including those censored for treatment discontinuation and those who received rescue therapy	34 (60.7%)	17 (30.9%)

EAG comments

- 23.2% in vehicle cream arm and 12.7% in the ruxolitinib arm censored due to treatment discontinuation
  - unclear reasons for discontinuation → plausible could be due to efficacy or safety of treatment
- 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
- EAG calculated relapse rates in each arm to include those who discontinued from the trial and/or those who received rescue medication (i.e. received ruxolitinib to maintain a response)

Abbreviations: CI, confidence interval; F-VASI, facial Vitiligo Area Scoring Index; ITT, intention-to-treat; NE, not estimable

EAG critique on TRuE-V studies and TRuE-V LTE

TRuE-V1 and TRuE-V2 pooled results

- 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 trials
  - relative effect estimates for all outcomes during the double-blind trial phases are most reliable for determining the effectiveness of ruxolitinib cream

TRuE-V LTE

- Trial did not represent the whole target population of people eligible to receive ruxolitinib (as in the parent trials) but instead represented a subset who tolerated treatment → selection bias in trial
- Threshold used to determine response (F-VASI90) was higher that the threshold for a response used by the company elsewhere in the submission (F-VASI75) and supported by clinical advice to the EAG

Abbreviations: F-VASI, facial Vitiligo Area Scoring Index

Health-related quality of life (HRQoL)

EQ-5D data was not collected in the TRuE-V trials

VitiQoL (Vitiligo-specific quality of life instrument)

- No statistically significant difference in scores was reported between groups at the end of the double-blind phase (week 24) in TRuE-V1 or TRuE-V2
- Absolute change in HRQoL increased between week 24 and week 52, but no statistical tests were performed to determine if the change from baseline was statistically significant
- EAG did not identify a validated clinically minimally important difference for this measure and so could not determine if participants in either arm showed a clinically meaningful change in VitiQoL

HADS (Hospital Anxiety and Depression Scale)

- At baseline, means scores on the HADS anxiety and depression subscales were within normal range
- Company considered that there was a numerically greater improvement in the HADS total score of depression and anxiety
- EAG considered this change was not statistically significant and was below published thresholds for a clinically meaningful change in HADS in any population
- EAG considered that there was no difference in HADS score between those receiving ruxolitinib and vehicle cream at 24 weeks and no benefit of ruxolitinib on HADS at 52-week follow-up

Adverse events

Adverse events in TRuE-V pooled trials (occurring in ≥ 1% in any treatment group)

- Ruxolitinib was associated with a small increase in the risk of adverse events compared to vehicle cream:
  - most common events with ruxolitinib cream included application site acne (5.8%), application site pruritus (5.1%), nasopharyngitis (4.2%), headache (3.8%) and upper respiratory tract infection (2.9%)
  - most events were mild in nature
  - the rate of adverse events increased between weeks 24 and 52
- Ruxolitinib cream was associated with a small increase in the rate of serious adverse events but none of these events were considered to be related to treatment

EAG comments

- People using ruxolitinib cream who experience application site adverse events may be more likely to discontinue treatment or change the application of ruxolitinib cream to another area of the body
- Oral ruxolitinib has been associated with an increased risk of non-melanoma skin cancer (NMSC) in other skin conditions
- No skin cancer events occurred in the TRuE-V or TRUE-V LTE trials. SmPC for ruxolitinib cream states that:
  - follow-up in trials was insufficient to determine whether NMSC may develop over time
  - people on ruxolitinib cream should be monitored for skin cancer, pending further evidence

Abbreviations: SmPC; summary of product characteristics

Feasibility of indirect treatment comparison

Background

- Company concluded that there was an insufficient evidence base to robustly compare the efficacy of ruxolitinib to existing therapies (topical 1st line treatments and phototherapy) because:
  - lack of comparable studies partly due to an evolving set of tools that are used to evaluate vitiligo
  - most of the clinical studies included in the feasibility assessment were of low methodological quality

EAG comments

- EAG assessed feasibility of conducting an ITC to compare ruxolitinib to phototherapy plus topical corticosteroids using the HI-Light trial (large, placebo controlled RCT, conducted in the UK)
- EAG agreed 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

Abbreviations: ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis; RCT, randomised controlled trial

How company incorporated evidence into model

Input	Assumption and evidence source
Baseline characteristics	Prior therapy subgroup (n=411), pooled TRuE-V1 and TRuE-V2
Ruxolitinib and vehicle cream* efficacy	**TRuE-V1 and TRuE-V2 pooled data (prior therapy subgroup data)** • initial response, sustained response, discontinuation **TRuE-V long-term extension (full trial population)** • Cohort A: relapse, retreatment (regain response and loss of response following retreatment) • Cohort B: retreatment (no regain response)
Utilities	• EQ-5D data was not collected in TRuE-V trials • EQ-5D-3L mapped from F-VASI and VitiQoL
Costs and resource use	• NHS Reference Costs, PSSRU, BNF, published literature, clinical expert opinion, previous NICE submissions
Treatment waning effect	No treatment waning assumed (loss of treatment response will lead to treatment discontinuation, which the company consider is a suitable proxy for waning)
Adverse events (AEs)	• Includes AEs costs that occurred in ≥4% of participants in the double-blind (24-week) period of TRuE-V1 and TRuE-V2 studies • Disutility due to AEs not included

*Vehicle cream = modelled as Uvistat Sun Cream SPF 50

Abbreviations: BNF, British National Formulary; EQ-5D, EuroQol 5-dimension; PSSRU, Personal Social Services Research Unit; VitiQoL, vitiligo-specific quality of life instrument

Approach to handling missing data for no regain of response

Background

- No regain response (F-VASI<75 at week 52 and F-VASI<90 at week 104) estimate is derived from TRuE-V LTE study (Cohort B)
- Applied as a 4-week (model cycle) probability estimate → company accounted for missing data in analysis:
  - approach applied average of 2 methods: method 1) removing missing data from overall sample of those with F-VASI<75 at week 52 and method 2) treating missing data as non-responders

EAG comments

- Method 1 assumes that non-responders were missing at random, which is a strong assumption applied without sufficient evidence, but applied correctly
- Method 2 did not treat missing data as non-response data but instead miscategorised the missing data entries as responses
- It is more appropriate to assume that missing data is indicative of non-response than missing at random, and EAG favoured this approach over company approach

Link to Differences between company and EAG preferred assumptions

Abbreviations: F-VASI, facial Vitiligo Area Scoring Index; LTE, long-term extension

Unknown impact, likely large

Key issue: Model structure and use of clinical data

Structural issue/ transition	EAG suggested impact of issue
Transition from initial period → non-response	*Underestimates the proportion who would continue treatment (and accumulate health benefits and costs) after 24 weeks*
Patients cannot improve and exit non-response	*Overestimates the proportion in non-response health state (which is associated with the lowest patient utility and higher costs)*
Patient in maintenance with a F-VASI 75-89 cannot advance to stable	*Underestimates the proportion of people in the stable health state (which is associated with the highest patient utility and lowest cost)*
Retreatment with vehicle cream is not aligned with NHS practice	*Underestimates accumulated health benefits and costs associated with retreatment with an active therapy*

EAG comments (2)

- 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
- The proportion of patients receiving ruxolitinib in the model remaining on maintenance treatment at 1 year is less than 25%. This does not reflect the TRuE-V trials (around 80%) or expected clinical practice
- Disagree with modelled comparator and the treatment pathway as does not reflect NHS practice
- EAG has little confidence in the results of the model → only able to present tentative base case results

Abbreviations: F-VASI, facial Vitiligo Area Scoring Index; SmPC, summary of product characteristics

Link to Model structure and use of clinical data

Large impact

Key issue: Dosing assumptions

Link to Dosing assumptions

Background

- Company stated that it was not possible to provide anonymised patient-level dosing data at clarification but provided summary data (see table below)

Summary of ruxolitinib cream exposure in TRuE-V1 and TRuE-v2

	Ruxolitinib cream – TRuE-V1		Ruxolitinib cream – TRuE-V2	
Average weight of study drug applied daily (grams)	Double-blind period	Day 1 to Week 52	Double-blind period	Day 1 to Week 52
N	221	[redacted]	228	[redacted]
Mean (SD)	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]

EAG comments

- Mean higher than median daily ruxolitinib use (double-blind period [redacted])
- Standard deviation, minimum and maximum show variation of drug use across studies
- Some people in TRuE-V studies used more ruxolitinib than recommended in the SmPC

Abbreviations: SD, standard deviation; SmPC, summary of product characteristics

Moderate impact

Key issue: Utility values

Background

Absolute expected utility values applied in the company's model

- Utilities used to inform health states in the model were estimated using outputs from a regression analysis which included the covariates in the table below:

Description	Utility values applied in company base case
Baseline	0.879
No response	0.797
F-VASI50-74	0.890
F-VASI75-89	0.935
F-VASI90	0.945

Link to Utility values

Abbreviations: F-VASI, facial Vitiligo Area Scoring index

Company deterministic scenario analyses – key scenarios

Company scenario analyses (probabilistic) - ICERs include PAS discount for ruxolitinib cream

No.	Scenario (ruxolitinib cream versus vehicle cream, scenario applied to company probabilistic base case)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
1	**Company base case**	[redacted]	[redacted]	**14,676**
2	Utility data source for mapping to EQ-5D: Vitiligo Noticeability Scale (VNS)	[redacted]	[redacted]	398,929
3	Model time horizon: 10 years	[redacted]	[redacted]	5,687
4	Costs in the non-response state stop at: 5 years	[redacted]	[redacted]	39,272
5	Costs in the non-response state stop at: Lifetime	[redacted]	[redacted]	3,894
6	Population: Overall	[redacted]	[redacted]	19,179
7	Population: Fitzpatrick skin type IV-VI*	[redacted]	[redacted]	Dominant

***Company selected Fitzpatrick IV-VI categorisation because it considered that darker skin types are associated with a greater disease burden**

Abbreviations: ICER, incremental cost-effectiveness ratio; PAS; patient access scheme; QALY, quality-adjusted life year