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

Slides for committee – contains redacted information

Technology appraisal committee D [6 June 2024]

Chair: Megan John

Lead team: Matt Bradley, Carole Pitkeathley, Ben Searle

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

Technical team: Emily Leckenby, Adam Brooke, Janet Robertson

Company: Incyte

DG recommendation – January 2024

Ruxolitinib is not recommended, within its marketing authorisation, for treating non-segmental vitiligo with facial involvement in people 12 years and over

Reasons the committee made this decision:

- Uncertain how well ruxolitinib works compared with phototherapy; company provided no evidence to support comparison (DG 3.4, 3.5, 3.6)
- Assumptions in company's economic model do not reflect how vitiligo is treated in clinical practice (DG 3.7, 3.8)
- Not possible to determine a reliable cost-effectiveness estimate; beyond the scope of EAG's exploratory analyses to correct inappropriate modelling assumptions (DG 3.14)

Consultation responses received from:

- Incyte Biosciences (company) – **new evidence and base case provided**

Patient and clinical organisations:

- British Association of Dermatologists (BAD)
- British Dermatological Nursing Group (BDNG)
- Vitiligo Society
- Vitiligo Support UK

Experts:

- 1 x patient expert
- 1 x clinical expert

- **Web comments** (n=25)

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

- ✓ **Recap and key issues**
- ❑ Consultation responses
- ❑ Company response and EAG critique
- ❑ Cost-effectiveness analysis

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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

RECAP

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*

"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..."

*such costs are not specified in the NICE reference case

See appendix – Patient perspectives and Clinical perspectives

Equality considerations

RECAP

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

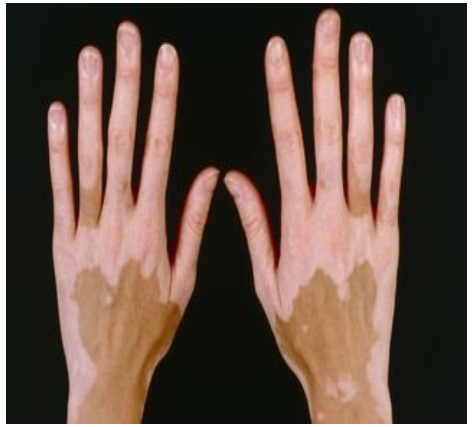


Figure 1: NSV
(source NHS health: vitiligo)

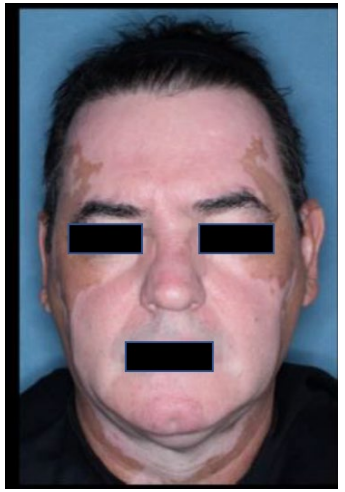


Figure 2: NSV
(source company submission)

The committee can only appraise ruxolitinib cream within its marketing authorisation

Abbreviations: NSV; non-segmental vitiligo

Ruxolitinib cream (Opzelura, Incyte)

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
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 NHS list price is 1 x 100g tube £657.00 [source Incyte website] • 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

See appendix – Ruxolitinib cream

Treatment pathway

RECAP

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

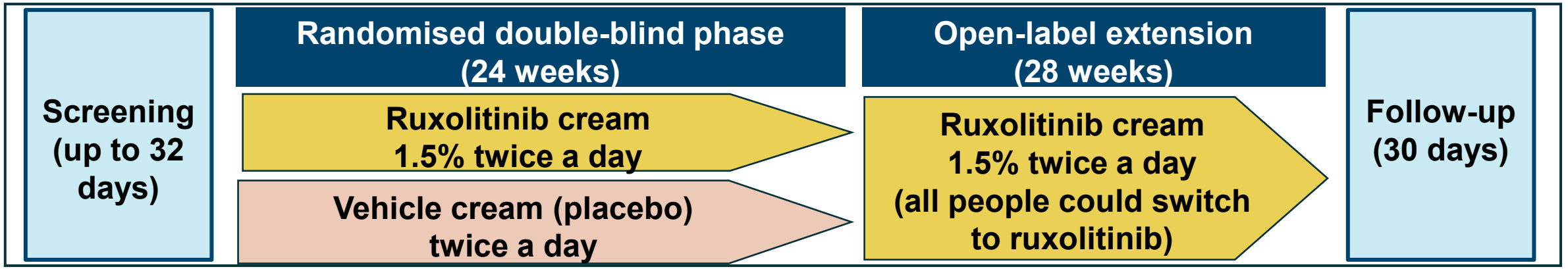
*can be given in alternation with topical tacrolimus for areas with thinner skin

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

Key clinical trials – TRuE-V1 and TRuE-V2

RECAP

	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

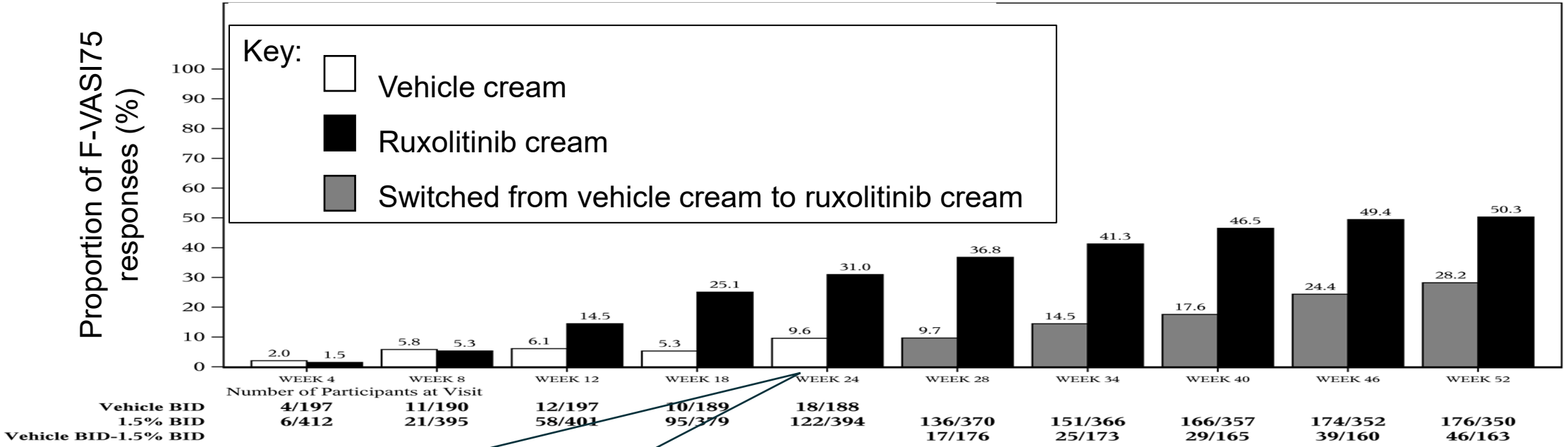
Abbreviations: BSA, body surface area; F-VASI, facial Vitiligo Area Scoring Index; T-VASI, total body Vitiligo Area Scoring Index

See appendix – Clinical section

TRuE-V1 and TRuE-V2 pooled results

RECAP

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

Committee preferred assumptions following ACM1

Economic model

- Committee determined that flaws in company's economic model biased results in favour of ruxolitinib, and therefore was not suitable for decision making. **Requested a model that:**
  - **Allowed for a direct comparison with phototherapy/NB-UVB**
  - **Reflected clinical practice more closely, as currently:**
    - definition of treatment discontinuation overestimated number of people discontinuing by 24 weeks
    - those in non-response state after ruxolitinib would not experience any improvement in condition
      - did not reflect those who would receive another active treatment
      - people should be able to transition from non-response state if improvement experienced
    - people receiving vehicle cream received re-treatment with vehicle cream upon relapse
    - company assumptions around use of NB-UVB in non-response state biased in favour of ruxolitinib
  - **Made changes to inputs to match preferred assumptions for costs, resource use, dosing (see slide 13)**

Abbreviations: NB-UVB, narrowband ultraviolet B

Committee preferred assumptions following ACM1 (2)

Revised economic model provided by company

- Initial response defined as >F-VASI25 at week 52 (>25% improvement in repigmentation = responders)
- People who achieve F-VASI90 at week 52 directly transition to stable health state
- Response is reassessed at week 104 (i.e., 2 years) as a one-off approach to align with the duration of the TRuE-V and long-term extension (LTE) studies and clinical practice.
  - F-VASI90 = move to the stable state
  - F-VASI<25 = move to the non-response state
  - F-VASI25-89 remain in the same health state (maintenance/retreatment period), where they stop treatment and gradually drop out to non-response over time
- Optional retreatment component (retreated and stable retreated health states) that people can enter following relapse from stable state – to acknowledge paucity of long-term comparative data
- A lifetime time horizon is applied to costs in the non-response health state
- A direct comparison with phototherapy, either as monotherapy or in combination with TCS, is incorporated
- 'Maintenance period' has been renamed to 'maintenance/retreatment period' to allow for different treatment schedules anticipated between ruxolitinib and NB-UVB

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Abbreviations: F-VASI, facial vitiligo area scoring index; NB-UVB, narrowband ultraviolet B; TCS, topical corticosteroids

Committee preferred assumptions following ACM1 (3)

Key Issue	Committee preferred assumption	Revised by company?
Comparators (DG 3.4)	• Comparative effectiveness evidence against phototherapy	• **Yes** – MAIC provided using published data from HI-Light
Dosing (DG 3.9)	• Present individual patient-level body surface area and dosing data from TRuE-V trials	• **Yes** – also updated base-case assumption to estimated mean daily dose of treatment
Resource use (DG 3.10/3.11)	• Revise assumptions of phototherapy, psychological support and dermatology attendance to reflect expected clinical practice	• **Yes** – disease management resource use assumptions revised to reflect committee preferences
Utility values (DG 3.12)	• Using a weighted average in the non-response health state of the values presented by the company for no response and having F-VASI 50 to 74	• **No** – updated definition of response from F-VASI75 to F-VASI25 - patients with F-VASI50 no longer defined as non-responders
Adverse events (DG 3.13)	• Incorporate utility and cost implications of adverse events (AEs) occurring in at least 1% of the population in any treatment group, including NB-UVB	• **No** – disagree with approach - majority of AEs experienced by patients in the TRuE-V trial treated with ruxolitinib were mild and transient

Abbreviations: F-VASI, facial vitiligo area scoring index; MAIC, matching-adjusted indirect comparison

Key issues remaining after ACM1

Issue	ICER impact
Positioning of ruxolitinib cream and comparators • Is the company's indirect comparison of ruxolitinib and phototherapy suitable for decision making?	**Large**
Model structure • Does the updated model reflect how vitiligo would be treated in the NHS if ruxolitinib was approved? • Do the proposed changes to the model structure appropriately reflect the anticipated use of ruxolitinib in clinical practice? • Are the assumptions around retreatment appropriate for decision making? • Why is time spent in F-VASI 90 different to the trial? • Are these clinical assessments reflective of how response and discontinuation would be monitored in clinical practice?	**Unknown**
Dosing • What dose of ruxolitinib is most appropriate?	**Large**
Adverse event assumptions • Why have utility and cost implications for AEs present in 1% or more of people in any treatment group not been incorporated in the model?	**Unknown**
Utility values • Are the EAG's revisions appropriate for decision making? • How should baseline and non-response utility values be modelled?	**Large**

Abbreviations: F-VASI, facial vitiligo area scoring index

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

- ❑ Recap and key issues
- ✓ **Consultation responses**
- ❑ Company response and EAG critique
- ❑ Cost-effectiveness results

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Consultation responses to draft guidance

Comments received from:

- **Patient and clinical organisations**
  - British Association of Dermatologists (BAD)
  - British Dermatological Nursing Group (BDNG)
  - Vitiligo Society
  - Vitiligo Support UK
- **Company**
  - Incyte Biosciences
- **Experts**
  - 1 x patient expert
  - 1 x clinical expert
- **Web comments** (n=25)

Response themes: clinical expert/organisations

Unmet need for treatment

- First ever treatment licensed for vitiligo; people in UK currently deprived of effective treatment option
    - Currently available treatments for vitiligo show only around 30-40% success rate
    - Early treatment seems to be more efficacious compared with treatment of long-standing disease

Suitability of comparators

- Concern that whole-body hospital phototherapy is considered a comparator
    - Systemic effect on whole skin, expensive to attend appointments, limited provision of services
- Hi-Light trial used 'limited' handheld phototherapy; theoretically could be compared to ruxolitinib, but is not considered reflective of clinical practice as handheld phototherapy is only offered by one hospital in England

Primary vs secondary care

- Almost half of people with vitiligo are initially misdiagnosed; initiation by GPs in primary care inappropriate
    - Often refuse to prescribe topical steroids/calcineurin inhibitors due to lack of experience
- Initiation of ruxolitinib in secondary care with possible shared care agreement more appropriate
    - Allows for adequate monitoring and management of side effects and adherence to BAD efficacy criteria

Abbreviations: BAD; British Association of Dermatologists; GP: general practitioner

Response themes: patient expert/organisations

Decision to not approve use of ruxolitinib is incorrect, based on untenable proposals and is inequitable

- Concern than committee decision does not reflect seriousness of vitiligo

Unmet need for treatment

- Currently available treatments are minimally effective as they are indicated for other skin conditions
    - Majority of patient community expressed need for more effective treatments, or a cure for vitiligo
- Condition is more noticeable in people with darker skin tones; group are at a greater disadvantage

Impact of disease

- Condition causes varying level of distress and can have a large impact on mental health
    - People feel “open to ridicule, stares, jibes and critique”
    - Large impact on self-esteem, profound psychological distress, need to use camouflage products
- Modern life means disease has large impact; physical differences even less well-tolerated than previously

Suitability of comparators

- Phototherapy is not a course of treatment that is “accessible, simple, controllable or low-cost”
    - Waiting lists for dermatology very long, preliminary appointment would require people to advocate for their referral to phototherapy; urgent conditions are often triaged as higher priority

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

- ❑ Recap and key issues
- ❑ Consultation responses
- ✓ **Company response and EAG critique**
- ❑ Cost-effectiveness results

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Key issue: Positioning and comparator assumptions (1)

Large

Background

- Committee concluded at ACM1: if positioned in secondary care, relevant comparators include phototherapy (with or without topical treatments), or no active treatment for those who are ineligible

Company response

- Clarified that ruxolitinib is being positioned as a secondary care option
- Provided cost-effectiveness analyses based for ruxolitinib vs NB-UVB (alone [1], or with TCS [2]), and ruxolitinib vs no active treatment (alone [4], or followed by NB-UVB [3])
- Presented a naïve (unweighted) and a matching-adjusted (weighted) indirect comparison with NB-UVB using data from Hi-Light; direct comparison of ruxolitinib with no active treatment based on ITT populations of pooled TRuE-V studies
- Comparing to no active treatment only doesn't reflect clinical practice
  - Conservative to assume that people who don't receive NB-NVB would never receive active treatment

EAG comments on positioning

- Difficult to qualify precisely which people would be considered 'not eligible' for NB-UVB
- If ruxolitinib made available in NHS, many people seeking treatment were likely currently receiving no active treatment, however some of these people may in future go on to receive NB-UVB

Abbreviations: ITT, intention to treat; NB-UVB, narrowband ultraviolet B; TCS, topical corticosteroids

Key issue: Positioning and comparator assumptions (2)

Large

Company response – ITC ruxolitinib vs NB-UVB

- Presented a naïve (unweighted) and a matching-adjusted (weighted) indirect comparison using data from Hi-Light
- Repigmentation scores used in Hi-Light and F-VASI used in TRuE-V were assumed reasonably equivalent measures of change in pigmentation from baseline
- Participants matched on age, sex and Fitzpatrick I-III
  - Comparison suggests that ruxolitinib has 7-8x higher odds of achieving overall response than NB-UVB

Modelled estimates (OR): ruxolitinib vs NB-UVB monotherapy at 9 months (wk 40)

F-VASI	MAIC estimates (weighted)
	Odds Ratio (SE) [95% CL; p-value]
0-24%	[redacted] p<0.001]*
25-100%	[redacted] p<0.001]*
50-100%	[redacted] p<0.001]*
75-100%	[redacted] p<0.001]*

EAG comments on ITC of ruxolitinib vs NB-UVB

- Commended company for attempting to make comparisons as requested by committee after ACM1
- No confidence in ITC results comparing ruxolitinib to NB-UVB, with/without topical corticosteroids due to:
  - Variation in baseline characteristics between Hi-Light and ruxolitinib trials
  - Differences in baseline characteristics between arms of the small Hi-Light trial
  - Discrepancies between baseline characteristics reported for each trial that could be used in matching
  - Meaningful differences in outcomes measured in each trial
- Focused cost-effectiveness analyses for ruxolitinib vs no active treatment alone or followed by NB-UVB

- Is the company's indirect comparison of ruxolitinib and phototherapy suitable for decision making?

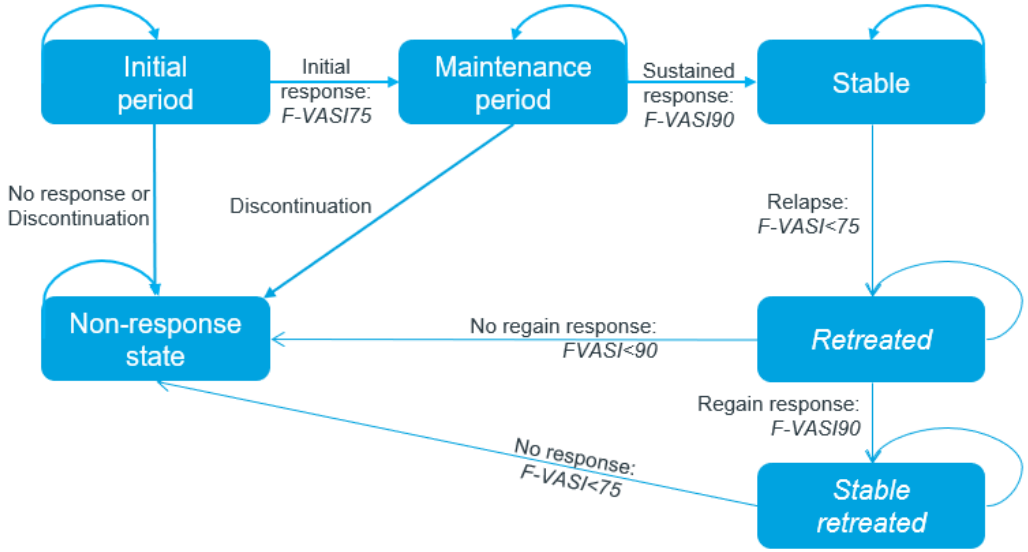
Abbreviations: CL, confidence level; F-VASI, facial vitiligo area scoring index; ITC; indirect treatment comparison, NB-UVB, narrowband ultraviolet B; OR, odds ratio; SE, standard error

Original model structure

Background (DG3.8)

- Committee agreed with EAG that there were flaws in company's model – not suitable for decision making
- Inappropriate modelling assumptions and use of clinical data from TRuE-V significantly biased cost-effectiveness results in favour of ruxolitinib

Committee requests after ACM1	Change?
Continuation does not match expected use - stopping should be considered if there is less than 25% repigmentation in treated areas at week 52.	Yes
People in non-response could not improve which would not reflect clinical practice. Costs incurred with no benefits	No
Structural error – people with F-VASI75 response could not transition to stable health state	Yes
Retreatment with the same topical treatment would not reflect NHS clinical practice.	Yes



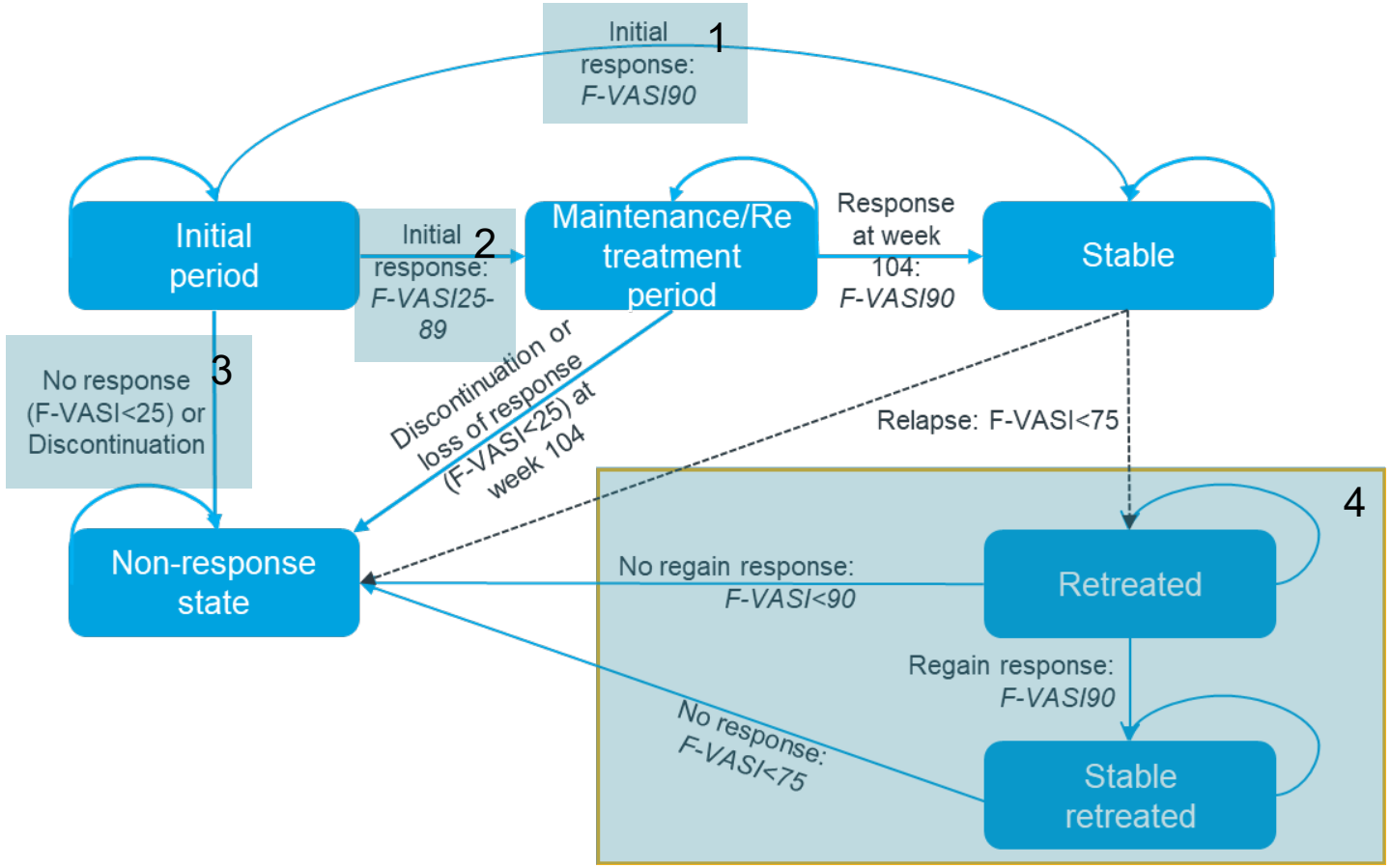
Abbreviations: DG, draft guidance; F-VASI, facial vitiligo area scoring index

Unknown

Key issue: Revised model structure

Company response – revised model

1. If response of F-VASI90 by week 52, people transition straight into the 'stable' health state
2. If response is between F-VASI25-89 by week 52, people transition to the 'maintenance/retreatment' phase for an upper limit of 52 weeks
   - Response reassessed by the end of this 52 weeks, and linked to response achieved at week 52
3. If F-VASI 25 not achieved by week 52, treatment was stopped, and people transition into the 'non-response' state
4. Optional retreatment state (100% eligible but only applies to approx. [redacted]% of people)
   - Criteria for retreatment differs markedly from initial treatment period



- Does the updated model reflect how vitiligo would be treated in the NHS if ruxolitinib was approved?

Abbreviations: F-VASI, facial Vitiligo Area Scoring Index

Unknown

Key issue: Revised model structure

EAG comments on revised company model

- Improvement on previous model and addressed number of concerns, however, still has limitations
- Not clear how model represents those who have minimal response by week 24
  - EAG clinical expert: expects clinical practice to be an assessment of response every 3-4 months, look for ~20% improvement in repigmentation to continue treatment
- In theory, when people enter 'retreated' state, they instantly leave according to F-VASI score – see next slide
  - In reality, people would be treated for a given time, followed by assessment of response
- When stable/stable retreated, people stop receiving ruxolitinib, leading to reduction in F-VASI score
  - Reduction to <F-VASI75 triggers movement from 'stable retreated' to 'non-response' state
  - Once they enter 'non-response' state, they remain there for lifetime of model
  - Unable to return to any previous states once deemed non-responsive to treatment
- People only permitted to undergo one course of retreatment with ruxolitinib or vehicle cream
  - Retreatment not viable option for vehicle cream
  - People may undergo several rounds of ruxolitinib
- As a result, model doesn't capture possibility of retreatment, and any starting and stopping rules associated with retreatment

- Do the proposed changes to the model structure appropriately reflect the anticipated use of ruxolitinib in clinical practice?

Abbreviations: F-VASI, facial Vitiligo Area Scoring Index

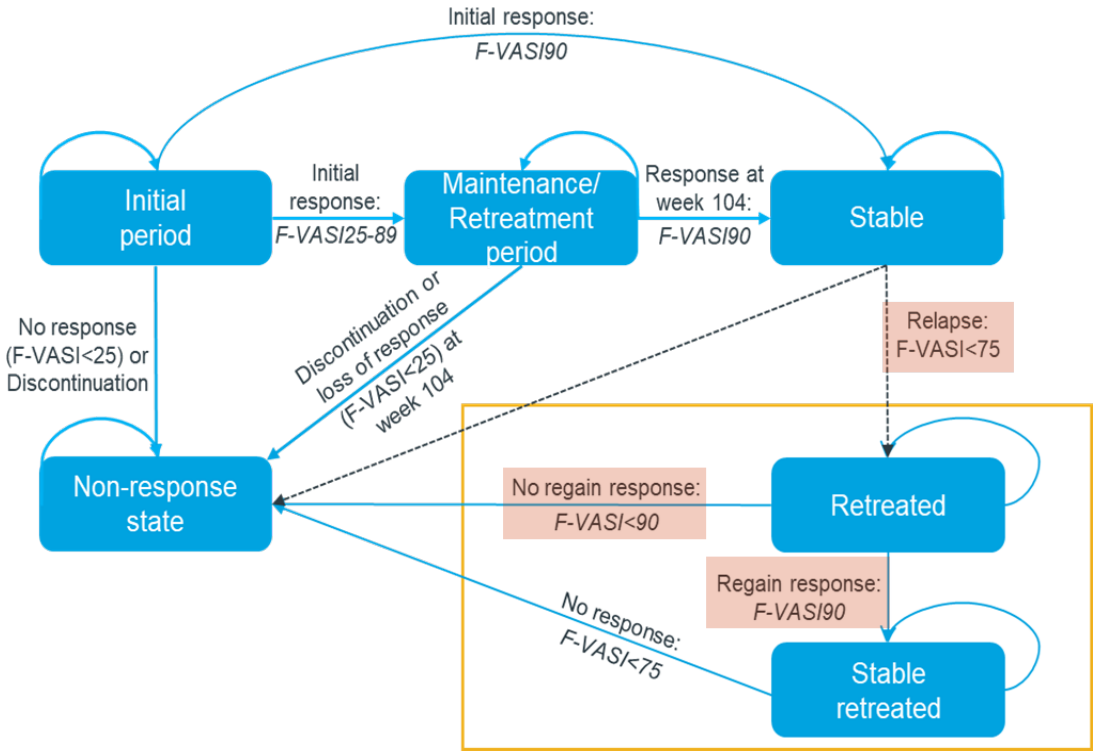
Unknown

Key issue – Revised model structure – retreatment

EAG comments on costs and QALYs associated with retreatment

- Not clear how retreatment was considered and questioned its validity – disaggregated results showed retreatment was associated with an additional cost of £[redacted] and an additional QALY gain of [redacted] applied to the ruxolitinib cream arm
- This can then be compared to the total costs and QALYs gained for the first course of treatment, which are £[redacted] and [redacted] (i.e. [redacted] QALYs for [redacted] of cost)
- EAG estimate that over the lifetime of the model, approximately [redacted]% of patients would initiate retreatment at some stage
  - People who entered the 'retreated' phase represented a sample of people for whom previous treatment led to an F-VASI90 response
- Provided scenario exploring infinite rounds of retreatment to explore structural

Red boxes denote the criteria used to determine which people can be retreated, and how they are later determined to exit the 'retreated' health state

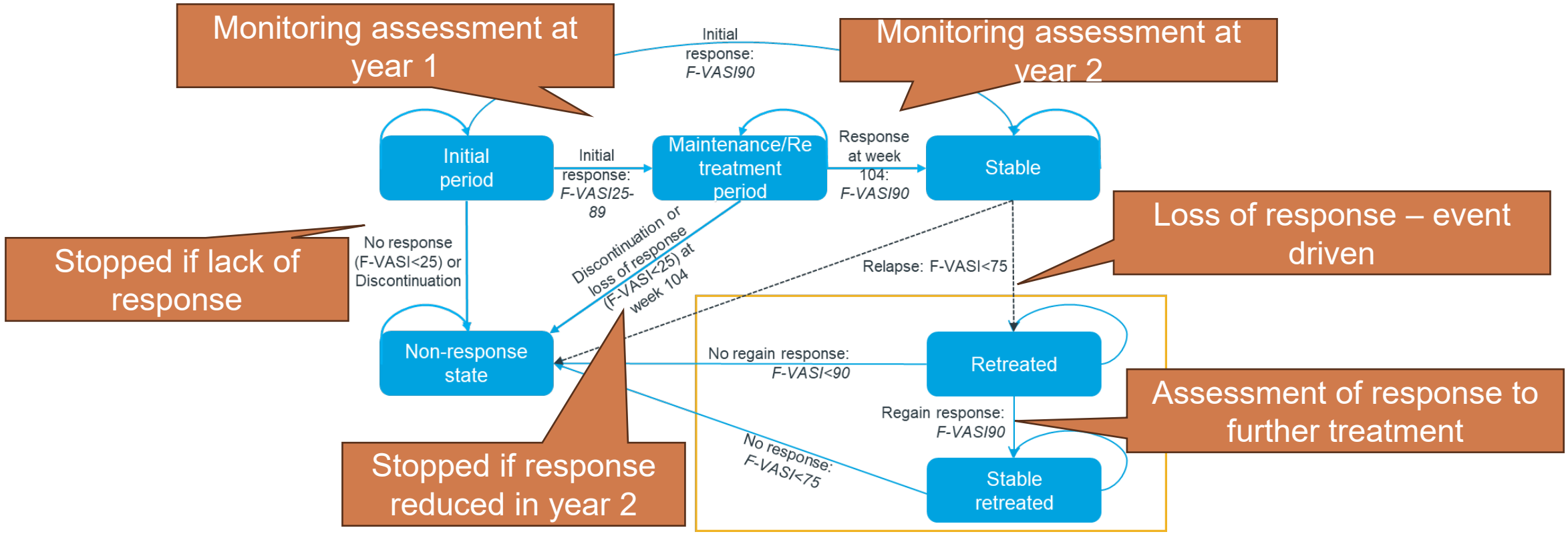


- Are the assumptions around retreatment appropriate for decision making?

Abbreviations: F-VASI, facial Vitiligo Area Scoring Index

Key issue: Revised model structure – monitoring

Unknown



- Are these clinical assessments reflective of how response and discontinuation would be monitored in clinical practice?

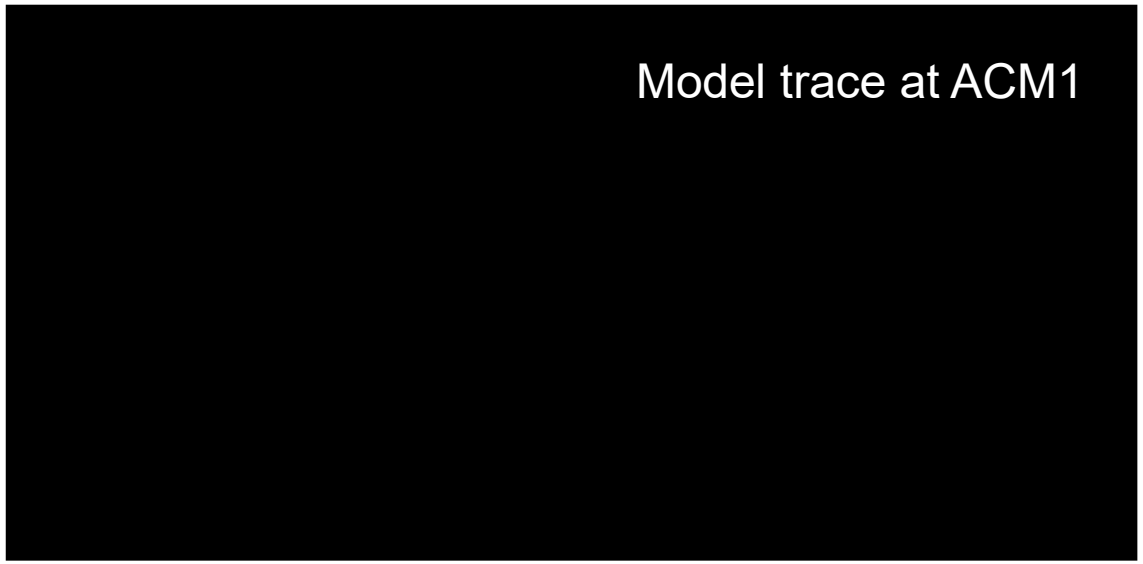
Abbreviations: F-VASI, facial Vitiligo Area Scoring Index

Unknown

Key issue: Revised model structure - validation

EAG comments on revised company model

- Markov traces used to visualise time spent in different model states; average additional time spent with F-VASI 90 approximately doubled; attempted to validate proportions by comparing with TRuE-V1, -V2, and LTE trials
- Estimated proportions at Week 104 noticeably dissimilar; unrealistic, would expect model values to be lower than trial values, and questioned validity of F-VASI 90 increasing between weeks 52 and 104
- Not a guarantee; proportion of people with F-VASI 90 in practice depends on how ruxolitinib use is managed



F-VASI 90 across both models and estimates from trials	Time	Original model	Revised model	TRuE-V
	Week 52	[redacted]	[redacted]	30.3%
	Week 104	[redacted]	[redacted]	18.7%

- Why is time spent in F-VASI 90 different to the trial?

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

Large

Key issue: Dosing assumptions

See appendix – Dosing assumptions

Background

- Committee concluded at ACM1: mean dose of ruxolitinib alone from pooled TRuE-V trials should be used in model, using appropriate methods to account for any missing data

Company response

- Updated dosing assumption to use mean daily dose of ruxolitinib from pooled TRuE-V, rather than median
- Explained there were nine people for whom missing data led to likely overestimation of daily dose:
  - For nine patients, duration of treatment was imputed as 1 day, with total weight of drug applied assumed to be same as their mean daily dose (which ranged between 117g and 237g)
- Revised mean dose informing company base case was [redacted]g/day; lognormal distribution fitted to TRuE-V trial dosing data in its entirety to avoid loss of information, while also accounting for the nine outliers
- Also provided new scenario in which nine outlier patients excluded from a simple re-calculation of the mean dose, leading to a value of [redacted]g/day, increased ICER

EAG comments on dosing assumptions

- Did not receive required information to validate company's lognormal distribution fitted to the data (numerical or graphical validation, as well as assessment of statistical goodness of fit)
- Could only justify use of the revised non-parametric estimate of the mean, using the value of [redacted]g/day
- Determining true cost of ruxolitinib to NHS difficult; several factors influence cost (overall intended use, dispensing practices, retreatment in NHS practice) – dose not necessarily linked to outcome in TRuE-V

- What dose of ruxolitinib is most appropriate?

Unknown

Key issue: Adverse event assumptions

See appendix – Adverse event assumptions

Background

- Company's analysis does not include HRQoL implications of 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
- Committee concluded that **company should incorporate utility and cost implications for AEs present in 1% or more of people** in any treatment group in the model, including those related to NB-UVB

Company response

- Majority of AEs experienced by people in TRuE-V treated with ruxolitinib were mild and transient
  - Not expected to affect QoL or lead to additional costs to the NHS that would impact cost-effectiveness
- Inclusion of costs and utility implications of AEs in model would likely favour ruxolitinib; any disutilities associated with AEs likely to be of greater magnitude with NB-UVB than ruxolitinib

Rates of AEs; people treated with ruxolitinib/no active treatment (TRuE-V) and NB-UVB (Hi-Light)

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

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

Unknown

Key issue: Adverse event assumptions (2)

EAG comments on adverse event assumptions

- Previously raised concerns at clarification and ACM1 about incorporation of utility and cost implications of AE data (occurring in 1% or more of people in any treatment group)
- 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:
  - 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

- Why have utility and cost implications for AEs present in 1% or more of people in any treatment group not been incorporated in the model?

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

Large

Key issue: Utility values – EAG revisions

See appendix – Utility values

Background

- Company's overall approach to derive health state utility values reasonable; EAG's revision to cap the utility values at general population values and to estimate utility for non-response health state appropriate

Company response

- Given the structural edits made to the company model, company updated its utility analysis to ensure values could be estimated for all necessary F-VASI thresholds used to determine health state occupancy
- Higher value for F-VASI25-49 vs 50-74 attributed to inability to discriminate in QoL between response categories

EAG comments on utility values

- Original range shorter; company revised model applies relatively greater disutility for non-responders
- F-VASI25-49 lacks validity
- Average utility for age and sex-adjusted gen pop aligned with trials estimated at ~0.908
- EAG edits ensure utility value for F-VASI25-49 is less than 50-74, and no values exceed value for gen pop

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

- Are the EAG's revisions appropriate for decision making?

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Abbreviations: F-VASI, facial vitiligo area scoring index; QoL, quality of life

Large

Key issue: Utility values – no response utility value

EAG comments on utility values

- No response state represents a wide variety of disease
  - Highly heterogeneous group, as includes people with small responses, people who with no change and people who experience disease progression
  - NB: 74% of trial participants had stable disease and a mean of 14.8 years since diagnosis
- Previously raised concerns about discrepancy between no response and baseline utility values
- Provided exploratory analysis with no response utility as either equal to baseline ([redacted]), or the average of no response and baseline utility values ([redacted])– large impact on ICER
- Large utility benefit if retreatment occurs; people avoid entering 'no response' state and therefore do not experience lower utility values

Revised utility analysis included additional category for F-VASI25-49, impacts no response health state as it no longer includes people with F-VASI25-49 improvement

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

- How should baseline and non-response utility values be modelled?

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Abbreviations: F-VASI, facial vitiligo area scoring index

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

- Recap and key issues
- Consultation responses
- Company response and EAG critique
- **Cost-effectiveness results**

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Company revised base case results

ICERs include PAS discount for ruxolitinib cream

Deterministic base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
NB-UVB [1]					
NB-UVB	[redacted]	[redacted]	-	-	-
Ruxolitinib cream	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
NB-UVB + TCS [2]					
NB-UVB + TCS	[redacted]	[redacted]	-	-	
Ruxolitinib cream	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
No active treatment followed by NB-UVB [3]					
No active treatment	[redacted]	[redacted]	-	-	-
Ruxolitinib cream	[redacted]	[redacted]	[redacted]	[redacted]	£18,103
No active treatment alone [4]					
No active treatment	[redacted]	[redacted]	-	-	-
Ruxolitinib cream	[redacted]	[redacted]	[redacted]	[redacted]	£20,018

Abbreviations: NB-UVB, narrowband ultraviolet B; TCS, topical corticosteroids

Differences between company and EAG preferred assumptions

	Company base case	EAG tentative base case
Comparators	• 4 comparisons presented: 1. Ruxolitinib cream versus NB-UVB 2. Ruxolitinib cream versus NB-UVB + TCS 3. Ruxolitinib cream versus no active treatment followed by NB-UVB 4. Ruxolitinib cream versus no active treatment	• Uses comparison 3 to determine base case
Utility values	• Utility values estimated through manipulation of trial data. Values generated for some health states above those of general population	• Utility values capped at general population in response states • F-VASI 25-49 edited as to not exceed F-VASI 50-75
Ruxolitinib dosing	• Mean from TRuE-V studies, with lognormal distribution to account for outliers	• Mean from TRuE-V studies; outlier patients excluded from a simple re-calculation of the mean dose

Abbreviations: F-VASI, facial vitiligo area scoring index; NB-UVB, narrowband ultraviolet B; TCS, topical corticosteroids

EAG tentative base case results

Deterministic results - include PAS discount for ruxolitinib
Uses comparison 3 (versus no active treatment followed by NB-UVB)

- Concerned that company's revised model **over-estimated the benefits and under-estimated the costs of ruxolitinib cream** through the following mechanisms:
  - Time spent in F-VASI 90 may be unrealistic
  - Utility gains likely inflated due to some utility values being greater than those for age- and sex-adjusted general population, as well as broader spread of utility values across different response categories
  - Only one course of retreatment was permitted, despite there being no apparent upper limit for treatment courses in expected NHS practice
- Taken together, alongside the EAG's tentative revised base-case analysis, **most likely ICER was expected to be greater than the range normally considered** to represent a cost-effective use of NHS/PSS resources

Scenario/EAG revisions (R) (Ruxolitinib cream versus no active treatment followed by NB-UVB)	Incremental results		ICER
	Costs (£)	QALYs	£/QALY
Company base case	[redacted]	[redacted]	**£18,103**
R1) F-VASI 25-49 utility value set equal to that of F-VASI 50-74	[redacted]	[redacted]	£18,154
R2) All utility values capped by general population utility estimates	[redacted]	[redacted]	£21,798
R3) Ruxolitinib cream dose to the revised mean, [redacted]g	[redacted]	[redacted]	£21,400
EAG tentative base case (R1-R3)	[redacted]	[redacted]	**£25,856**

Abbreviations: F-VASI, facial vitiligo area scoring index; NB-UVB, narrowband ultraviolet B

EAG exploratory analysis – retreatment assumptions

Deterministic results (unless otherwise stated) - ICERs include PAS discount for ruxolitinib cream
Uses comparison 3 (versus no active treatment followed by NB-UVB)

- EAG sought to understand the costs related to retreatment, and utility for the non-response state

Scenario (Ruxolitinib cream versus no active treatment followed by NB-UVB)	Incremental results		ICER
	Costs (£)	QALYs	£/QALY
Company base case	[redacted]	[redacted]	£18,103
Retreatment disabled for no active treatment arm	[redacted]	[redacted]	£17,726
Infinite retreatment enabled for ruxolitinib arm*	[redacted]	[redacted]	£3,037

*did not exhibit validity to be suitable for decision making, but helpful when considering impact of retreatment

Abbreviations: NB-UVB, narrowband ultraviolet B

EAG exploratory analysis – utility values

Deterministic results (unless otherwise stated) - ICERs include PAS discount for ruxolitinib cream
Uses comparison 3 (versus no active treatment followed by NB-UVB)

- EAG sought to understand the costs related to retreatment, and utility for the non-response state

Scenario (Ruxolitinib cream versus no active treatment followed by NB-UVB)	Incremental results		ICER
	Costs (£)	QALYs	£/QALY
Company base case	[redacted]	[redacted]	£18,103
No response utility same as baseline ([redacted])	[redacted]	[redacted]	£60,336
No response utility average of no response and baseline ([redacted])	[redacted]	[redacted]	£27,850
EAG tentative base case	[redacted]	[redacted]	**£25,856**
EAG tentative base case + no response utility same as baseline	[redacted]	[redacted]	£167,585
EAG tentative base case + no response utility average of no response and baseline	[redacted]	[redacted]	£44,800

Abbreviations: NB-UVB, narrowband ultraviolet B

EAG base case disaggregated results – ruxolitinib arm

*undiscounted

[redacted]

	Year 1	Year 2	Years 3 and onwards
QALY gain (compared to no response)	[redacted]	[redacted]	[redacted]
LY in F-VASI 90	[redacted]	[redacted]	[redacted]
LY on treatment	[redacted]	[redacted]	[redacted]
Ruxolitinib acquisition costs	[redacted]	[redacted]	[redacted]
Disease management costs (inc. phototherapy and other treatments)	[redacted]	[redacted]	[redacted]

Key issues remaining after ACM1

Issue	ICER impact
Positioning of ruxolitinib cream and comparators • Is the company's indirect comparison of ruxolitinib and phototherapy suitable for decision making?	**Large**
Model structure • Does the updated model reflect how vitiligo would be treated in the NHS if ruxolitinib was approved? • Do the proposed changes to the model structure appropriately reflect the anticipated use of ruxolitinib in clinical practice? • Are the assumptions around retreatment appropriate for decision making? • Why is time spent in F-VASI 90 different to the trial? • Are these clinical assessments reflective of how response and discontinuation would be monitored in clinical practice?	**Unknown**
Dosing • What dose of ruxolitinib is most appropriate?	**Large**
Adverse event assumptions • Why have utility and cost implications for AEs present in 1% or more of people in any treatment group not been incorporated in the model?	**Unknown**
Utility values • Are the EAG's revisions appropriate for decision making? • How should baseline and non-response utility values be modelled?	**Large**

Abbreviations: F-VASI, facial vitiligo area scoring index

Thank you.

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