Ritlecitinib for treating severe alopecia areata in people 12 years and over

For committee, experts, EAG and company – contains ACIC information

Technology appraisal committee A - 5 September 2023

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Company: Pfizer

Abbreviations

AAPPO
Alopecia areata patient priority outcomes

AE
Adverse event

AIC/BIC
Akaike/Bayesian information Criterion

AFT
Accelerated failure time

AT
Alopecia totalis

AU
Alopecia universalis

BSC
Best supportive care

CI
Confidence interval

EBA
Eyebrow assessment

ELA
Eyelash assessment

FDG
Final draft guidance

ICER
Incremental cost effectiveness ratio

KM
Kaplan Meier

RCT
Randomised controlled trial

SALT
Severity of Alopecia Tool

SD
Standard deviation

TE
Technical engagement

TEAEs
Treatment-emergent adverse events

TTO
Time trade off

VAS
Visual analogue scale

Background on alopecia areata

Autoimmune condition affecting scalp, face or body

Causes

- Immune system attacks hair follicles causing inflammation and premature transition of hair follicles from growth to loss phase – but exact cause unknown

Epidemiology

- UK estimates: around 0.58% of adults

Diagnosis and classification

- Usually presents as patches of baldness on scalp
- Alopecia totalis (AT): hair loss across whole scalp
- Alopecia universalis (AU): hair loss across whole body

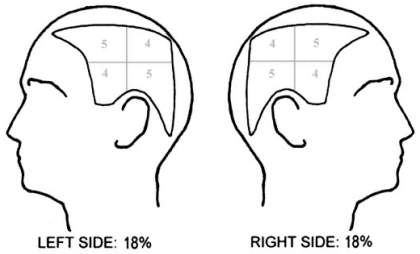
Prognosis

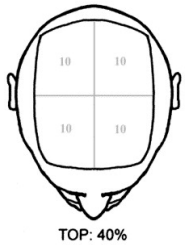
- Unpredictable and varied prognosis depending on severity and duration of condition

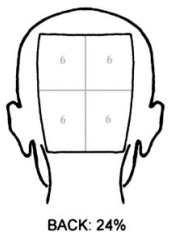
Classification of severity: Severity of Alopecia Tool (SALT)

Population in appraisal: severe alopecia areata

- % hair loss in 4 areas of scalp measured and multiplied by surface area
- Sum of 4 values provides total score







SALT 100 = complete scalp hair loss
SALT 0 = no scalp hair loss

Company defines severe alopecia areata as ≥50% scalp hair loss (SALT ≥50)

Absolute measure

SALT ≤20 = no more than 20% of scalp surface area hair loss

- Outcome in trial and used in model
- Validated as clinically meaningful
- Absolute SALT ≤20 difficult to achieve in very severe disease

Relative measure

$SALT_{50}$ = 50% reduction from baseline score

- Useful for measure of improvement in very severe cases
- Large amount of hair loss may still need camouflage

- SALT limitation: only assesses scalp hair loss
- Absolute measure (SALT ≤20) accepted outcome in baricitinib final draft guidance

Is absolute SALT score an appropriate measure to show clinical effect?

Ritlecitinib (Litfulo, Pfizer)

Technology details

Expected marketing authorisation (expected Oct 2023)	• [redacted]
Mechanism of action	• Small molecule that inhibits JAK3 and TEC kinase family, downregulating an overactive immune response at hair follicles
Dose	• [redacted]
Administration	• Oral monotherapy
Price	**List price:** • £[redacted] per pack of 30 capsules • [redacted] for 12 months of treatment Patient access scheme available

Patient perspectives

Ritlecitinib offers hope for a condition with wide ranging impact on psychosocial health

Submission from Alopecia UK

- Impacts include depression and anxiety, social isolation, absenteeism, bullying, stigma, and stress on relationships
- Many spend own money on products to adjust appearance – such as wigs, microblading and false eyelashes
- Lack of treatment options frustrating; clear unmet need
- Hair loss has significant impact in some cultures; appropriate wigs difficult to source for diverse hair types

Statement from patient expert

- Describing AA as cosmetic is inaccurate and insulting – impact on QoL can be devastating
- Stress on intimate relationships - hair loss has psychological impact on sex drive
- Need drugs that target AA specifically and not repurposed

"For me, there is no hope. Not having a licensed treatment in UK, specifically designed to tackle AA, adds to the darkness."

"Previously quite gregarious, I now restrict myself to a small circle of family and friends. I have turned down several offers of employment as I feel unable to face the wider world."

Clinical perspectives

Data suggests ritlecitinib improves hair growth across the scalp, eyebrows and eyelashes and is well tolerated

Submission from British Association of Dermatology (endorsed by Royal College of Physicians)

- Alopecia areata is a chronic autoimmune disease with significant psychological implications
- Significant unmet need for a new safe and effective medicine
- Time and financial pressures associated with current treatment
- Data indicates ritlecitinib is effective with good safety profile
- Ritlecitinib also helps regrow eyebrows and eyelashes, which is likely to be associated with improved QoL

Equality considerations

- Pivotal clinical trial includes people who have had AA for up to 10 years - recommendations should not be restricted by disease duration due to possibility of age discrimination
- Beard hair loss can have more severe implications for people with certain religious faiths
- Worse prognosis for adolescents
- Geographic variability in contact immunotherapy and wig provision – providing an effective systemic treatment with geographic equity may address this (if recommended, treatment should be available in all secondary care dermatology sites)
- HRQoL measures may not capture impact of AA for older people or people not in a relationship

Key issues for discussion

Key issues raised by EAG:

Issue	ICER impact
Source of utility values	High
Carer disutilities	Small
Alopecia totalis/ universalis (AT/AU) subgroup	Moderate
ICER not based on weighted average of outcomes for adults and adolescents	Small
Long term transition matrices – treatment effect waning	Small
Rates of ritlecitinib discontinuation results in long mean time on treatment	Small

Additional key issue

Issue	ICER impact
Definition of established clinical management and appropriate comparator	Unclear

Decision problem

Company's decision problem aligns with final scope

Population, intervention, comparators and outcomes from the scope

	Final scope	Company
Population	People aged 12 years and over with severe alopecia areata	As in scope: severe AA defined as SALT ≥50
Intervention	Ritlecitinib	Ritlecitinib
Comparators	Established clinical management without ritlecitinib	Non-pharmacological treatment
Outcomes	• Severity of AA • % area affected • Adverse effects • HRQoL	• Response rate based on SALT ≤20 or ≤10 at week 48 • Change in SALT score • Patient global impression of change • TEAEs • HRQoL (EQ5D, VAS, SF-36)

Current treatment: severe alopecia areata

No licenced treatments for severe alopecia areata currently available in NHS; lack of consensus for optimal management

Severe alopecia areata

Secondary care treatment options:

- Topical corticosteroids
- Contact immunotherapy (DCPC)
- Systemic treatment - immunosuppressants and oral corticosteroids
- Wigs

Options vary by patient and are dependent on age (adolescent or adult)

Company:

- Topical steroids impractical for extensive hair loss
- Contact immunotherapy not widely available
- Limited evidence of efficacy and safety concerns for systemic treatment

BSC comparator defined by company as non-pharmacological therapy (includes wigs)

Clinical experts:

- Limited disease treated with topical corticosteroids
- Contact immunotherapy used in some centres
- Systemic therapies used for extensive disease

What is the appropriate comparator (how is established clinical management defined)?

Clinical effectiveness

NICE National Institute for Health and Care Excellence

Key clinical trials: ALLEGRO 2b/3

	ALLEGRO 2b/3
Design	RCT
Population	• People aged ≥12 with severe AA (SALT ≥50) • Current episode ≤10 years • No evidence of re-growth within previous 6 months
Intervention	Subgroup of interest: ritlecitinib 50mg (licensed dose) once daily (n=130)
Comparator	Placebo (2 arms: dose escalation [200/50mg] (n=65) + continuous dose [50mg]) (n=66)
Duration	Placebo controlled: 24 weeks; total: 48 weeks
Primary outcome	Response rate based on SALT ≤20 at week 24
Key secondary outcomes	SALT ≤20 at week 48; SALT ≤10 at week 24 and 48; patient's global impression of change; eyebrow and eyelash assessment; HRQoL
Locations	155 sites globally (10 in the UK)
Use in model	Informs health state occupancy for ritlecitinib (48 weeks) and best supportive care (24 weeks)

Key clinical trials: ALLEGRO-LT

	ALLEGRO-LT
Design	Single-arm, open-label, long-term study
Population	• Participants exiting ALLEGRO 2a* or 2b/3 plus *de novo* participants • People aged ≥12 with SALT score ≥25 (*de novo* population) • Current episode ≤10 years
Intervention	ALLEGRO 2a or 2b/3 roll-over: ritlecitinib 50mg once daily De novo: ritlecitinib 200mg 4 week loading dose followed by 50mg once daily
Duration	36 months
Primary outcome	Incidence of adverse events (including serious AEs and AEs leading to discontinuation)
Secondary outcome	Response rate based on SALT ≤20
Locations	148 sites globally (4 in the UK)
Use in model	Informs health state occupancy from week 48 for those who continue ritlecitinib

*ALLEGRO 2a: proof of concept study

ALLEGRO 2b/3 clinical effectiveness results (1)

Greater improvement in SALT score with ritlecitinib compared with placebo over 24 weeks; continued improvement with ritlecitinib up to week 48

Response based on SALT ≤20 up to week 48

Response rate (% with SALT ≤20) at week 24:
Ritlecitinib 50mg (n=130): [redacted]
Placebo (n=131): [redacted]
% difference (95% CI): [redacted]

Response rate (% with SALT ≤20) at week 48:
Ritlecitinib 50mg (n=130): [redacted]

Placebo arms switched to ritlecitinib

Longer term clinical effectiveness results

Longer follow up from ALLEGRO 2b/3 and ALLEGRO-LT suggests continued improvement after 24 months with ritlecitinib

Ritlecitinib 50mg QD (combined cohort*):
N=191

ALLEGRO 2b/3 50mg ritlecitinib cohort only,
48-week response rate (SALT ≤20): [redacted]

*combined cohort: treated with 50mg ritlecitinib for 48 weeks in ALLEGRO 2b/3 and 50mg ritlecitinib in ALLEGRO-LT or treated with placebo for 24 weeks and 50mg ritlecitinib for 24 weeks in ALLEGRO 2b/3 and 50mg in ALLEGRO-LT

ALLEGRO 2b/3 clinical effectiveness results (2)

Greater improvement in patient's global impression of change and eyebrow + eyelash assessment with ritlecitinib compared with placebo over 24 weeks

Outcome	Ritlecitinib 50mg	Placebo*	% difference (95% CI) †
Eyebrow assessment (≥2 grade improvement from baseline or score of 3) at week 24, n/N (%)	[redacted]	[redacted]	[redacted]
Eyelash assessment (≥2 grade improvement from baseline or score of 3) at week 24, n/N (%)	[redacted]	[redacted]	[redacted]
Patient's global impression of change response (moderately or greatly improved) at week 24, n/N (%)	[redacted]	[redacted]	[redacted]

* combined multiple placebo arms

† missing data due to COVID-19 excluded from analysis; participants with missing data due to other reasons considered non-responders

Clinical experts:

- Current care with contact immunotherapy is site specific – ritlecitinib shows eyelash and eyebrow regrowth too

ALLEGRO 2b/3 HRQoL results

EAG:

- Little change in HRQoL scores from baseline to week 24 or 48 across range of measures
- Baseline HRQoL scores generally indicate participants have good HRQoL at start of study

Outcome	Ritlecitinib 50mg n=130	Placebo 200/50mg N=65	Placebo 50mg N=66
EQ-5D-5L baseline (adults), mean (SD)	[redacted]	[redacted]	[redacted]
EQ-5D-5L week 24 (adults), mean (SD)	[redacted]	[redacted]	[redacted]
AAPPO emotional symptoms score baseline, mean (SD)	[redacted]	[redacted]	
AAPPO emotional symptoms score week 24, mean (SD)	[redacted]	[redacted]	

AAPPO: patient reported outcome tool; 5-point scale, lower scores better

HRQoL data collected in ALLEGRO 2b/3 (not all reported here):

- EQ-5D-5L (adults), EQ-5D-Y (children), EQ VAS, SF-36 (physical and mental components), HADS (anxiety and depression components) and AAPPO (hair loss, emotional symptoms and activity components)

ALLEGRO 2b/3 subgroup results: adolescents and adults

No indication of differences between adolescent and adult subgroups in SALT score

Response rate (participants with SALT score ≤20) at week 24, n/N (%)	Ritlecitinib 50mg	Placebo	% difference (95% CI)
Age 12 to 17 years	[redacted]	[redacted]	[redacted]
Age ≥18 years	[redacted]	[redacted]	[redacted]

Company

- Adolescent and adult subgroups have [redacted] response rates
- Clinicians state no difference in treatment effect expected between adults and adolescents

Do the results for adolescents and adults align with experience in clinical practice?

ALLEGRO 2b/3 subgroup results: alopecia totalis/ universalis

May be a difference in effect between people with AT/AU and without AT/AU

Response rate (participants with SALT score ≤20) at week 24, n/N (%)	Ritlecitinib 50mg	Placebo	% difference (95% CI)
AT/AU	[redacted]	[redacted]	[redacted]
Non-AT/AU	[redacted]	[redacted]	[redacted]

Company

- AT/AU subgroup: statistically significant increase in response rate with ritlecitinib 50mg compared with placebo in both subgroups

EAG

- AT/AU and non-AT/AU subgroups: [redacted]

Clinical expert

- People with AT/AU less likely to have complete regrowth from treatments
- AT/AU population makes up ~half of ALLEGRO 2b/3 total population

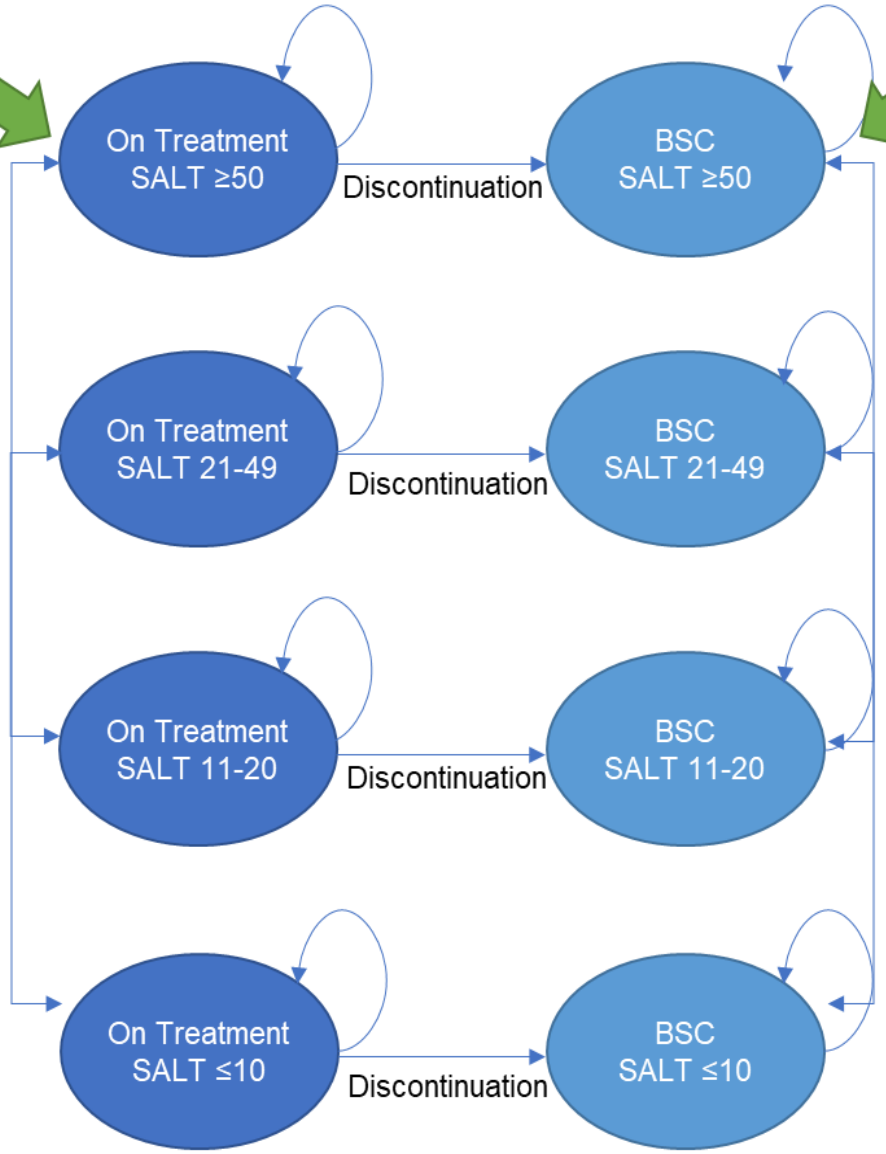
Cost effectiveness

NICE National Institute for Health and Care Excellence

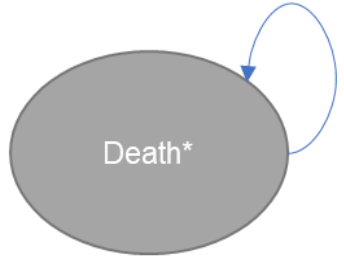
Company's model overview

Patients treated with ritlecitinib enter here and can move between all health states

- Ritlecitinib data (ALLEGRO 2b/3 and LT) informs first 96 weeks – then no change until discontinuation or death
- Discontinuation (informed by ALLEGRO 2b/3 and LT) – if SALT worsened at 24 weeks or if SALT >20 at 48 weeks or any point after: move to equivalent BSC state and then transition to SALT ≥50 (worsening 1 health state every cycle); time on treatment informs long-term discontinuation



Patients on BSC enter here and can move between BSC health states



- Placebo data (ALLEGRO 2b/3) informs first 24 weeks (2 cycles)
- After week 24: those with improved SALT score transition back to SALT ≥50 (worsening 1 health state every cycle)

Company's model overview

Technology affects **costs** by:

- increasing costs for ritlecitinib acquisition
- reducing costs for managing AA by reducing time spent with severe AA
- increasing costs associated with adverse events
- increasing costs associated with monitoring

Technology affects **QALYs** by:

- improving HRQoL by reducing time spent with severe AA and increasing time spent with mild to moderate AA
- improving carer HRQoL
- increasing HRQoL losses associated with adverse events

- Choice of utilities source is assumption with greatest ICER effect
- Other assumptions have small to moderate impact

How company incorporated evidence into model

Input	Assumption and evidence source
Baseline characteristics	**ALLEGRO 2b/3:** • Adults ([redacted]%) and adolescents ([redacted]%) • Adults mean age: [redacted] adolescents mean age: [redacted]
Utilities	**Company's vignette study:** • Utility for severity-based health states • Carer (of adolescents) disutility
Resource use	**Expert opinion:** • Wigs, psychological support consultation, visits to dermatology nurses, GPs and dermatologists – included in ritlecitinib and BSC health states at varying rates across states and arms
Costs	• Ritlecitinib acquisition – **PAS price** • Monitoring – **National Schedule of NHS Costs 20/21** • Wigs and visits to healthcare team - **Expert opinion, National Schedule of NHS Costs 20/21 & PSSRU 2021** • Management of adverse events - **National Schedule of NHS Costs 20/21**

Model does not include use of any pharmacological treatment options following non-/loss of response – does this reflect clinical practice?

Key issue: Utilities (1)

High impact

Company: EQ-5D lacks content validity and is insensitive in AA

Background

- Clinical trial collected EQ-5D but not used to generate utilities in economic model

Company

General issues with EQ-5D:

- Lacks content validity: no domains on social functioning, relationships, emotional impact, physical appearance and financial impact
- Insensitive to changes in HRQoL related to AA severity - will under-estimate benefits
- Baricitinib FDG suggests that EQ-5D may not capture important aspects of the condition
- Caution against comparing with other skin conditions to evaluate EQ-5D construct validity

Issues with trial EQ-5D:

- High proportion report no problems on EQ-5D at baseline – ceiling effect makes showing improvement in HRQoL difficult
  - could be due (for example) to high level of adaptation (average time since diagnosis 10.1 years) or exclusion of people with depression

Key issue: Utilities (2)

High impact

EAG: company did not convincingly demonstrate that EQ-5D not appropriate in AA

EAG comments

- Some elements impacted by AA would map well to EQ-5D: worry, sadness, anxiety and hopefulness (anxiety and depression domain); academic performance/ productivity (usual activities domain)
- Assessment of EQ-5D responsiveness to treatment in AA is limited to ritlecitinib trials
  - ALLEGRO 2b/3 may be too short to demonstrate responsiveness; company did not provide longer term EQ-5D data from ALLEGRO-LT
  - high baseline EQ-5D in ALLEGRO 2b/3 may be due to selection bias
- Data showing variation in EQ-5D scores by AA severity (mild, moderate, severe) in Adelphi* data suggests EQ-5D is sensitive to different disease severity
  - statistically significant difference in EQ-5D by severity of AA (including in anxiety/depression domain alone) in Japanese cohort study of Adelphi data
  - European cohort data reporting limited, but utilities consistent with Japanese cohort

EAG uses European cohort Adelphi data (Bewley et al.) to estimate utility values

*Adelphi AA Disease Specific Programme – real world evidence database

Key issue: Utilities (3)

High impact

Company: EAG has not provided enough evidence to support the claim that EQ-5D fully captures HRQoL impact in AA

Company

Issues with published EQ-5D preferred by EAG (Adelphi data, Bewley et al.):

- Not aligned with SALT model health states – Adelphi uses mild, moderate, severe grading based on clinician judgement therefore subject to bias
- Literature does not support assumption that EQ-5D is capturing all the burden of AA
- Inconsistent to use Adelphi data when EAG suggested that trial-based EQ-5D utilities are underestimated

Company uses vignette study to estimate utilities for each health state

Key issue: Utilities – company's vignette approach (1)

High impact

EAG: analysis based on vignette should be treated with caution

Company's vignette approach

1. Draft vignettes – informed by QoL data in ALLERGRO 2b/3, interviews (3 adults, 3 adolescent patients, 5 carers) and lit review

2a. Feedback on draft vignettes (5 adult patients, 5 carers and 4 healthcare professionals)
2b. Vignettes for 4 SALT score ranges developed

3. Vignettes reviewed and rated by UK general public using TTO (n=120) and utilities estimated for each health state

EAG comments

Best practice methods for vignette development followed, but concerns around:

- vignettes don't report absence of symptoms unaffected by AA such as self-care and mobility - may lead to overestimation of importance of condition-specific symptoms by general public in TTO
- patients interviewed required to have had specific treatments or be interested in systemic treatment – doesn't capture people not actively seeking treatment who may have lower HRQoL impact from severe AA
- vignettes lack face validity compared with data in ALLEGRO 2b/3 (see next slide)

Abbreviations: TTO, time-trade off; (HR)QoL, (health-related) quality of life; SALT, Severity of Alopecia Tool; AA, alopecia areata

Key issue: Utilities – company's vignette approach (2)

High impact

EAG: vignettes lack face validity compared with ALLEGRO 2b/3 data

Comparison of vignette for person with SALT 50-100 and responses to HRQoL AAPPO questionnaire in ALLEGRO 2b/3 in SALT 50-100 population

Vignette SALT 50-100	ALLEGRO 2b/3 AAPPO item response SALT 50-100	
[redacted]	**Over the past week, how often did you feel embarrassed about your hair loss?**	Never/ rarely: [redacted] Sometimes: [redacted] Often/ always: [redacted]
[redacted]	**Over the past week, how often did you feel frustrated about your hair loss?**	Never/ rarely: [redacted] Sometimes: [redacted] Often/ always: [redacted]
[redacted]	**Over the past week, how much did you limit your exercise or other physical activity because of your hair loss?**	Not at all/ a little: [redacted] Moderately: [redacted] A great deal/ completely: [redacted]

Abbreviations: AAPPO, alopecia areata patient priority outcomes; HRQoL, health-related quality of life; SALT, Severity of Alopecia Tool

Key issue: Utilities – company's vignette approach (3)

High impact

Company: vignette study methodology follows best practice - deviation would risk bias

Company

- Vignettes used multiple sources to reduce bias – ALLEGRO AAPPO data only 1 source
- Exploratory interviews suggested impact of AA was greater than described in ALLEGRO
- ALLEGRO excluded people with suicidal ideation or depression, so data may under-estimate impact of AA
- Focus should be on people with AA who are interested in receiving treatment, therefore excluding people not seeking treatment appropriate

Abbreviations: TTO, time-trade off; (HR)QoL, (health-related) quality of life; SALT, Severity of Alopecia Tool; AA, alopecia areata

Key issue: Utility values used in model

High impact

Utility values generated from vignette study and from Bewley et al. (2022) EQ-5D

Health state (SALT)	Utilities, mean	
	Vignette (company base case)	Bewley et al. 2022* (EAG base case)
0-10	[redacted]	[redacted]
11-20	[redacted]	[redacted]
21-49	[redacted]	[redacted]
50-100	[redacted]	[redacted]

*Bewley et al. reported values for mild (0.90), moderate (0.85) and severe AA (0.78); EAG matched to model health states shown in table

Clinical experts

- EQ-5D does not capture impact of AA (supported by patient expert)
- Patients feel need to convince others they are well as hair loss associated with cancer treatment – may affect reporting of impact of condition

Baricitinib FDG committee conclusions:

- Severe and mild EQ-5D subgroup data from Adelphi to inform change in baseline after treatment is suboptimal
- True utility values likely to lie between BRAVE (baricitinib clinical trial EQ-5D) and Adelphi data – range considered for decision making

Are the utility values estimated from the vignette and Bewley et al. plausible?

Key issue: Utility generation methods - NICE manual

High impact

"To make the case that EQ-5D is inappropriate, provide qualitative empirical evidence on lack of content validity, supported by evidence that EQ-5D performs poorly on tests of construct validity and responsiveness.

Evidence should be derived from synthesis of peer-reviewed literature"

"If evidence shows EQ-5D not appropriate then use, in order of preference:

- *Other generic preference-based measure*
- *Condition-specific preference-based measure*
- ***Vignettes***
- *Direct valuation of own health"*

- Has the company justified deviation from EQ-5D as specified in the reference case?
  - Which source of utility estimates is most appropriate to include in the model?

Key issue: Carer disutilities

Small impact

Company applies carer disutility for carers of adolescents with severe AA

Background

- Carer disutility of [redacted] applied for carers of adolescents with severe AA (SALT ≥50)
  - Calculated by difference between utilities estimated from carer vignette and TTO approach ([redacted]) and UK population norm for people aged 35-44 (0.91)
- Assumed no carer disutility for carers of adolescents with mild to moderate (SALT <50) AA

Company

- Appropriate to consider impact on carers
- Accepted at TE to apply disutility to carers of adolescents only, to reflect vignette

EAG

- Impact on carers may continue for people with mild to moderate AA, i.e. due to concerns around treatment safety or symptom return
- Methods guide requires evidence to show substantial effect on carer's HRQoL – no utilities directly measured in carers provided; relies on carer vignette

Patient expert: Impact on carer can be severe, including through strain on relationships

Is it appropriate to include carer disutility of [redacted] for carers of adolescents with severe AA?

Key issue: alopecia totalis/universalis subgroup analysis

Moderate impact

ICER for AT/AU population higher than without AT/AU

ICER for weighted average of proportion expected to be AT/AU lower than pooled population

Background

- AT and AU subgroups specified in NICE scope

Company

- Provided AT/AU subgroup analysis at TE as well as weighted ICER based on proportion of AT/AU expected in clinical practice (9.52% - lower proportion than in ALLEGRO [46%])

EAG

- Updated analysis at TE broadly appropriate
- Subgroup specific data used for 48-week efficacy data and long-term transition matrices
- Other inputs such as discontinuation, utilities and resource use have not been updated to be specific to AT/AU status

NICE

Is it appropriate to consider a subgroup with AT/AU separately?

Key issue: ICER does not use weighted average of outcomes for adults and adolescents

Small impact

Background

- Company uses average baseline characteristics across the ALLEGRO 2b/3 population rather than modelling outcomes separately for adolescents and adults

EAG

- EAG prefers to model outcomes separately for adults and adolescent to accurately capture expected outcomes in these groups
- Weighted average can then be used to generate ICER for the whole population

Company

- Age does not modify treatment effect
- Adolescent subgroup uses ALLEGRO 2b/3 efficacy data for adults and adolescents – trial results for adults are over-represented when using weighted average approach

Is a weighted average of outcomes appropriate for determining the ICER?

Key issue: treatment effect waning (1)

Small impact

Background

- Company assume stable SALT for full time horizon for people on treatment after 96 weeks

Company

- Assumption of no treatment effect waning supported by ALLEGRO-LT trial data – further interim data provided at TE
- Clinicians support assumption of no treatment waning after 2 years treatment
- No alternative data to challenge assumption of long-term effect

Clinical experts

- Other long-term treatment (immunosuppressants) for severe AA tends to achieve static efficacy at around 12 months
- Chronic disease with unpredictable relapses with ongoing maintenance treatment; triggers such as infection may destabilise people with steady SALT score

Key issue: treatment effect waning (2)

Small impact

EAG

- Agrees proportion achieving SALT ≤20 remains stable (no evidence of treatment effect waning) up to 24 months
- **But** - limited follow-up in ALLEGRO-LT so hard to verify long term effect
- Unclear how missing data has been dealt with in interim analysis – appears to be treated as missing at random
- High proportion of missing data at 24 months ([redacted]% of cohort who started on 50mg dose missing) – less complete data beyond 24 months means if assume missing data is due to non-responders, proportion of responders falls after 24 months
- Prefers to use average transition matrices from second year of treatment to estimate long term outcomes for people remaining on treatment after 96 weeks

Is it appropriate to include treatment effect waning for people with stable SALT score on treatment after 96 weeks?

Key issue: time on treatment (1)

Small impact

Company uses Weibull model to extrapolate time on treatment

Company

- Discontinuation hazards shows AFT model needed; chooses Weibull based on AIC/BIC and fit to KM data
- Change in hazards at 1.4 years thought to be driven by a reduction in participant numbers
- High retention for ritlecitinib responders validated by dermatologists

EAG

- Apparent increase in discontinuation after 1.4 years not adequately explained by company
- Doesn't appear that latest data cut from ALLEGRO-LT has been used for long-term discontinuation analysis
- Low rate of discontinuation in company's model leads to predicted mean time on treatment of 5.9 years – longer than JAK inhibitors in other disease area

[redacted]

Key issue: time on treatment (2)

Small impact

EAG: visual fit of all extrapolations to time on treatment KM data are similar

Time on treatment Kaplan Meier data overlayed with different extrapolation curves

Key issue: time on treatment (3)

Small impact

EAG: large differences in long-term time on treatment extrapolation curves mean it is highly uncertain

Long-term time on treatment extrapolation curves

Key issue: time on treatment (4)

Small impact

EAG uses exponential model to extrapolate time on treatment

EAG continued

- No reason to select 1 parametric model over another (AFT model not needed as company states); little difference in AIC/BIC figures or visual fit to KM
- Uses exponential distribution for base case (lowest AIC/BIC and stable hazards up to 1.4 years), and explores other extrapolations

Clinical expert

- Non-dermatological disease JAK inhibitor discontinuation not suitable to predict discontinuation in AA
- Reasons to stop treatment include treatment failure, family planning and side effects

Which extrapolations for time on treatment should be considered in the model?

Cost effectiveness results

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Company base case results

Company deterministic base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	14,290

Company probabilistic base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	14,450

No confidential discounts included in the model other than intervention PAS

Company subgroup analyses

Company subgroup analyses (deterministic)

Company base case subgroup	Incremental costs (£) versus BSC	Incremental QALYs versus BSC	ICER (£) versus BSC
Company base case - whole cohort	[redacted]	[redacted]	14,290
AT/AU population (SALT 100 at baseline)	[redacted]	[redacted]	16,625
Non-AT/AU population (SALT <100 at baseline)	[redacted]	[redacted]	13,304
Weighted average according to expected distribution of people with AT/AU (9.52%) and non-AT/AU	[redacted]	[redacted]	13,526*
Age ≥18 years	[redacted]	[redacted]	15,312
Age ≥ 12 to 18 years	[redacted]	[redacted]	13,773

* calculated by NICE, weighting incremental costs and QALYs for each subgroup before calculating ICER (as opposed to company approach to weighting ICERs for each subgroup, resulting in company ICER of 13,620 for this subgroup)

EAG scenario analyses (on company base case)

EAG scenario analyses (deterministic) – uses average baseline characteristics and pooled outcome data across both age subgroups (company preferred approach)

	Scenario (applied to company base case)	Incremental costs (£) versus BSC	Incremental QALYs versus BSC	ICER (£) versus BSC
	Company base case	[redacted]	[redacted]	14,290
1	**Utilities from Bewley et al. (Adelphi study)**	[redacted]	[redacted]	41,199
	Changed from: utilities from vignette			
2	**Average transition matrices from second year of treatment used to estimate long term effect**	[redacted]	[redacted]	16,980
	Changed from: staying in state until discontinuation			
3	**Exponential curve to extrapolate treatment discontinuation**	[redacted]	[redacted]	14,358
	Changed from: Weibull curve			
	Cumulative changes scenario 1 to 3	[redacted]	[redacted]	47,812

EAG base case results

Deterministic base case results – combines EAG scenarios 1 to 3 and uses weighted mean of the outcomes for individual subgroups (EAG preferred approach)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Ritlecitinib	[redacted]	[redacted]			
BSC	[redacted]	[redacted]	[redacted]	[redacted]	48,987

Probabilistic base case results – combines EAG scenarios 1 to 3 and uses weighted mean of the outcomes for individual subgroups (EAG preferred approach)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Ritlecitinib	[redacted]	[redacted]			
BSC	[redacted]	[redacted]	[redacted]	[redacted]	50,123

EAG subgroup analyses

EAG subgroup analyses (deterministic unless stated otherwise)

EAG base case subgroups (and subgroup scenarios)	Incremental costs (£) versus BSC	Incremental QALYs versus BSC	ICER (£) versus BSC
EAG base case - whole cohort	[redacted]	[redacted]	48,987
Age ≥18 years	[redacted]	[redacted]	50,203
Age ≥18 years (probabilistic)	[redacted]	[redacted]	51,415
Age ≥ 12 to 18 years	[redacted]	[redacted]	43,269
Age ≥ 12 to 18 years (probabilistic)	[redacted]	[redacted]	44,073
AT/AU population (SALT 100 at baseline)	[redacted]	[redacted]	59,616
Non-AT/AU population (SALT <100 at baseline)	[redacted]	[redacted]	42,557
Weighted average according to expected distribution of AT/AU (9.52%) and non-AT/AU	[redacted]	[redacted]	43,461

EAG deterministic scenario analysis

EAG scenario analyses (deterministic)

Scenario (applied to EAG base case)	Incremental costs (£) versus BSC	Incremental QALYs versus BSC	ICER (£) versus BSC
EAG base case	[redacted]	[redacted]	48,987
Gompertz curve to extrapolate treatment discontinuation	[redacted]	[redacted]	49,551
Log-normal curve to extrapolate treatment discontinuation	[redacted]	[redacted]	48,412
No carer disutility	[redacted]	[redacted]	50,138
Transition matrices from month 21 to 24 used to estimate long term effect	[redacted]	[redacted]	53,593

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Thank you.