Baricitinib for treating severe alopecia areata

For PUBLIC – contains NO ACIC information

Technology appraisal committee A [7th February 2023]

Chair: Radha Todd

Lead team: Peter Baker, Min Ven Teo, Alan Thomas

Evidence assessment group: BMJ Technology Assessment Group

Technical team: Sharlene Ting, Eleanor Donegan, Janet Robertson

Company: Eli Lilly

Key issues

Submissions
- Company (Eli Lilly)
- Alopecia UK
- British Association of Dermatologists

Responses to technical engagement
- Company (Eli Lilly)
- British Association of Dermatologists
- Experts: 2 clinical and 2 patient

No.	Issues
1	Population: incident vs prevalent; severe vs very severe
2	Positioning of baricitinib
3	Relevant comparators: “Watch and Wait” (monitoring) vs “No active treatment” (no monitoring)?
4	SALT clinically meaningful outcome: SALT ≤20 vs $SALT_{75}$ vs $SALT_{50}$
5	Best supportive care: composition; proportion who will have BSC after no treatment response → variable for baricitinib vs no active treatment?
6	Source and dataset for utilities: BRAVE EQ-5D vs Adelphi EQ-5D vs BRAVE HADS?
7	Adverse events not modelled

EQ-5D, EuroQol-5 dimensions; HADS, Hospital Anxiety and Depression Scale; SALT, Severity of Alopecia Tool

Key clinical issues

- What is considered standard of care for people with severe alopecia areata?
    - What are the relevant comparators for people with severe alopecia areata? (no licensed options)
- What comprises best supportive care for people with severe alopecia areata whose condition has not responded after all possible treatment options have been exhausted?
    - What proportion of people with severe alopecia areata would continue to have best supportive care after all possible treatment options have been exhausted?
    - Would use of best supportive care be different depending on whether person had baricitinib or 'no active treatment'?
    - In which setting are best supportive care treatments commissioned?
- Where would baricitinib likely be used in the current treatment pathway
- Are the findings from the BRAVE trials that included people with more severe disease not from Europe generalisable to people likely to have baricitinib in NHS clinical practice?
- What is a clinically meaningful difference in SALT score in severe alopecia areata? An absolute measure SALT ≤20 (no more than 20% of scalp surface area involved) or a relative measure $SALT_{50 \text{ or } 75}$ (50% or 75% reduction in scalp surface area involved compared to baseline)?

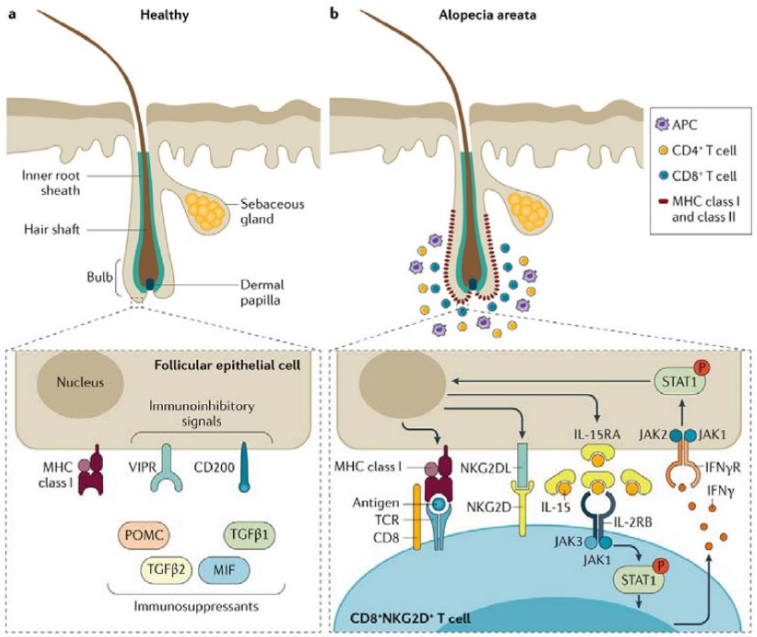
NICE

SALT, Severity of Alopecia Tool

Background on alopecia areata

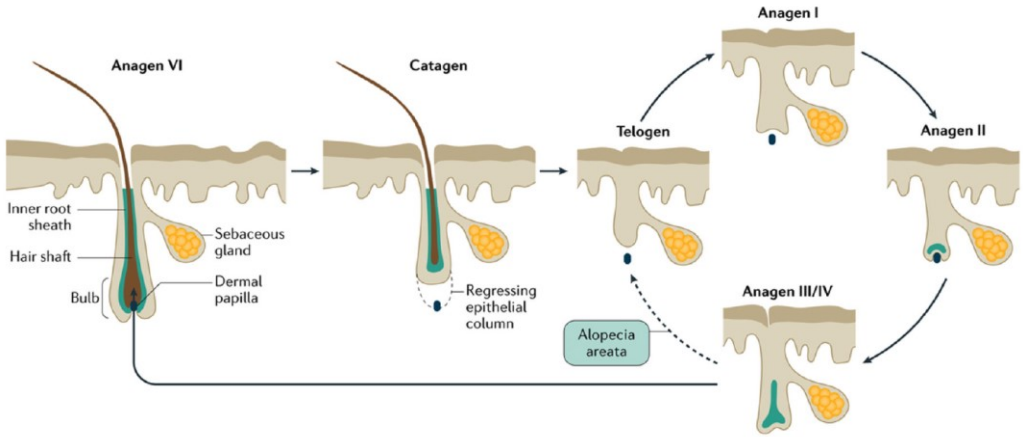
Autoimmune condition affecting scalp, face or body; exact aetiology is unknown

Classification and type depend on location and extent of hair loss e.g. patchy, totalis, universalis



Breakdown of immune privilege of hair follicles

Non-scarring hair loss (hair follicle preserved): changes in hair cycle, follicle size, breakage



Rapid progression of hair follicles from anagen phase to catagen and telogen phases

UK estimates in 2018 (study of 4.16m adults)

point prevalence 0·58%

0·26 per 1000 person-years incidence

m, million

Patient perspectives

Alopecia areata can have a large psychological impact

Submission from Alopecia UK

- Can affect all aspects of a person's life:
  - emotional wellbeing, difficulty coping, feelings of shock, trauma, loss of control (unpredictable condition), disrupted identity, isolation, hopelessness and sometimes suicidal thoughts; high levels of anxiety (36%) and depression (29%)
  - ability to work, study (absenteeism), socialise (bullying), take part in leisure activities, have intimate relationships
  - financial impact (healthcare services, treatments and camouflage options)
  - stigma and lack of understanding by others to recognise psychosocial impacts can exacerbate effect on quality of life
    - 25% told by healthcare professionals AA is 'just a cosmetic issue'
  - totalis and universalis may affect temperature regulation, nasal secretions, other hair such as eyebrows, eyelashes
- Auto-immune condition that is poorly understood with no cure and no real effective treatments; referral to dermatology variable with long waiting times; distressing when hair loss reoccurs when treatments stop

"They tell me to avoid stress but I can't turn off my life"

"I've been given a scalp ointment which I've had before and has little chance of working"

Clinical perspectives

Significant unmet need for safe and effective treatment for severe alopecia areata

Submission from the British Association of Dermatologists

- Chronic, autoimmune condition with significant psychosocial implications (social isolation, work absenteeism, illness-induced career change, loss of income, loneliness, failure to establish relationships, relationship breakdown, anxiety, depression, suicidal ideation)
- Significant unmet, clinical need for safe, effective and approved medicines for people with moderate-to-severe disease
- Clinically significant treatment response: at least a 50% reduction in hair loss ($SALT_{50}$), improvement in quality of life and significant patient-rated hair growth (able to stop wearing a wig/camouflage)
- Baricitinib initial trial data suggest treatment is effective, with a good safety profile; can address scalp, eyebrow/eyelash and body hair loss
- Long-term outcomes in AA are unpredictable

"Many hair specialists advocate earlier treatment to prevent progression to more extensive disease"

"It is difficult to truly capture the impact of treatments for AA using QALYs"

AA, alopecia areata; QALY, quality-adjusted life year; SALT, Severity of Alopecia Tool

Classification of severity: Severity of Alopecia Tool (SALT)

Differing views on clinically meaningful SALT outcome

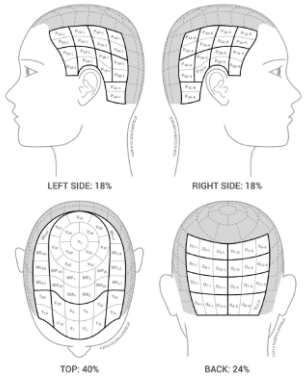
Absolute measure

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

SALT ≤20

- Clinically meaningful
- Overly restrictive
- Concomitant pattern baldness: ceiling effect
- Unlikely to capture continued hair regrowth after 36 weeks
- Absolute SALT ≤20 difficult in very severe disease (SALT 95–100); SALT ≤50 may have significant impact on QoL

SALT ≤10: very clinically meaningful for most; stop need for wigs



SALT II

0% = no hair loss

100% = total hair loss

Relative measure

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

$SALT_{50}$

- Clinically meaningful vs unclear if clinically meaningful → large amount hair loss may still need camouflage

$SALT_{75}$

- Patient-rated critical criteria used in BAD AA guidelines
- In severe disease, nearly equivalent to SALT ≤20

Other considerations: general satisfaction; SALT estimates imprecise → caution against strict thresholds (e.g. SALT ≤20, $SALT_{50}$) to stop treatment

What is a clinically meaningful outcome in SALT for severe alopecia areata? Company and EAG used SALT ≤20 in base cases

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AA, alopecia areata; BAD, British Association of Dermatologists; QoL, quality of life; SALT, Severity of Alopecia Tool

Baricitinib (Olumiant, Eli Lilly)

First licensed treatment for severe alopecia areata

Marketing authorisation	• Treatment of severe alopecia areata in adults • Granted by MHRA in October 2022
Mechanism of action	• Selective and reversible inhibitor of Janus kinase (JAK) 1 and JAK2; enzymes involved in inflammatory disease process
Administration	• Oral tablet • Recommended dose: 4mg once daily • Lower dose: 2mg once daily for people ≥75 years, history of chronic or recurrent infections, or people whose condition has shown sustained control with 4mg dose and are eligible for dose tapering • For stable response, continue treatment for several months to avoid relapse • Stop treatment after 36 weeks if no evidence of therapeutic benefit
Price	• List price of a 28-tablet pack of 2mg or 4mg is £805.56 • Annual cost is £10,508 • Patient access scheme applies

MHRA, Medicines and Healthcare products Regulatory Agency; JAK, Janus kinase

Treatment pathway

Baricitinib first licensed option for severe alopecia areata

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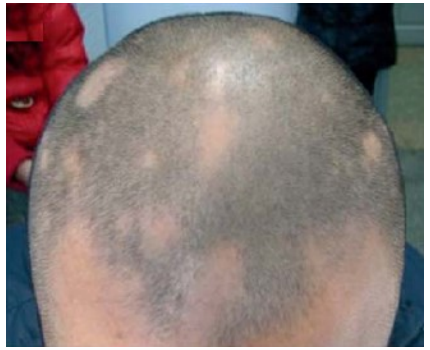
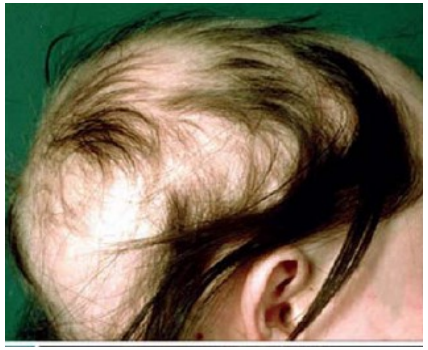


- No treatment / watchful waiting
- Advice on cosmetic options to camouflage hair loss

SEVERE

SALT ≥50



Baricitinib?

Primary care: topical corticosteroids

Baricitinib?

Referral to dermatologist (all off-label options):

- *local steroid injections or oral corticosteroids*
- *dithranol*
- *contact sensitisation treatment (contact immunotherapy)*
- *psoralen plus ultraviolet A light therapy (PUVA)*
- *minoxidil*
- *immunosuppressive drugs (e.g. oral azathioprine, ciclosporin, methotrexate, sulfasalazine)*
- *prostaglandin analogues (e.g. bimatoprost, latanoprost)*

Baricitinib?

Where is baricitinib likely to be used in NHS practice?

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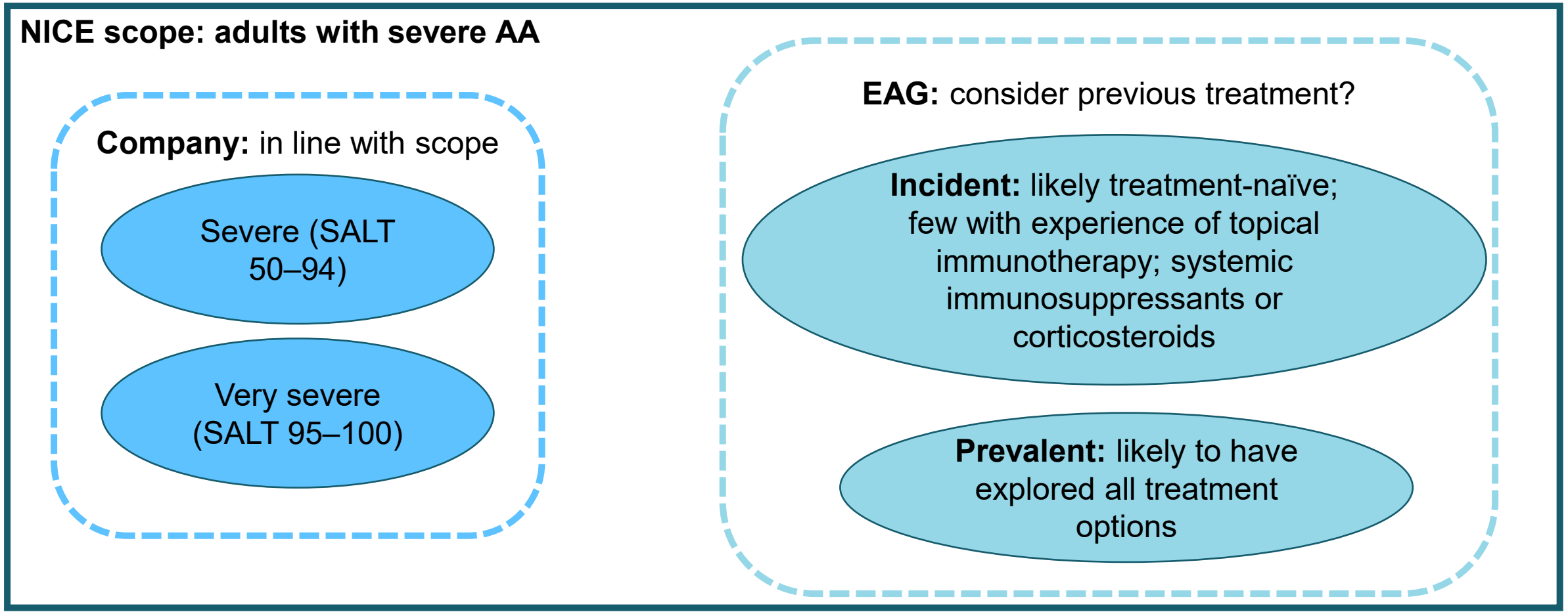
SALT, Severity of Alopecia Tool

Decision problem: population

EAG: BRAVE trial population may differ to NHS patients likely to have baricitinib, excluded baseline AA episodes >8 years; >60 years (males) or >70 years (females)

Intervention and outcomes are in line with scope



AA, alopecia areata; SALT, Severity of Alopecia Tool

Decision problem: comparators

Differing views on relevant comparators

NICE scope: established clinical management without baricitinib

Company and EAG used 'no active treatment' in base case

- No established standard of care/management pathway for severe AA
- Indirect comparisons not possible
- Treatment varies based on setting, availability, patient preference
  - ➢ Plausible option (6 months waiting time for dermatologist) vs very few people opt for no treatment

'Watch and wait' (no treatment, frequent monitoring)

- Not standard option

Common previous treatments:

- Topical / intralesional steroids

Newly diagnosed severe AA:

- Systemic immunosuppressants / steroids (commonly used)
  - ➢ Not established standard of care – limited effectiveness

BAD recommended:

- Topical immunotherapy (variable/inequitable access; scalp only)
- Wigs

What are the relevant comparators for people with treatment-naïve severe alopecia areata?
What are the relevant comparators for people with treatment-experienced severe alopecia areata?

AA, alopecia areata; BAD, British Association of Dermatologists

Clinical effectiveness

NICE National Institute for Health and Care Excellence

BRAVE-AA1 and BRAVE-AA2

No European or UK centres; phase 3 data (baricitinib 4mg and placebo) included in model

	BRAVE-AA1 – adaptive phase 2/3	BRAVE-AA2 – phase 3
Location	55% USA, 38% South Korea, 8% Mexico	35% USA, 27% Asia, 38% other
Sample	N=654	N=546
Design	multi-centre, randomised, double-blind, placebo-controlled, parallel-group	
Population	Adults (age: male ≤60; female ≤70) with severe AA: • current AA episode >6 months and SALT ≥50 at visits 1&2 • no spontaneous improvement in past 6 months ($SALT_{\leq 10}$) • current AA episode <8 years (if ≥8 years, enrol if regrowth observed) **Excluded:** 'diffuse' and other AA; conditions that could interfere with study; inadequate washout of drugs; previous inadequate response to ≥12 weeks of oral JAK-inhibitors	
Comparison	Baricitinib once daily (4mg, 2mg) vs placebo	
Duration	200 weeks (3 to 35 days screening, 36-week treatment, 68-week long-term extension, 104-week bridging extension, 28-day post-treatment follow-up)	
Outcomes	**Primary:** proportion with SALT ≤20 at week 36 **Key secondary:** other SALT thresholds at week 12, 16, 24 and 36; ClinRO for eyebrow and eyelash hair loss at week 36; PRO scalp hair assessment score; EQ-5D; Skindex-16 AA domain; Hospital and Anxiety Depression Scale; adverse events	

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AA, alopecia areata; ClinRO, clinician-reported outcome; EQ-5D, EuroQol-5 dimensions; JAK, Janus kinase; n, number; PRO, patient-reported outcome; SALT, Severity of Alopecia Tool

BRAVE baseline characteristics

Population had severe and difficult to treat AA; trials may underestimate treatment effectiveness vs NHS

Characteristic	BRAVE–AA1		BRAVE–AA2	
	Baricitinib (n=281)	Placebo (n=189)	Baricitinib (n=234)	Placebo (n=156)
Atopic background, %	35	39	37	43
Duration of current AA episode				
Mean (SD)	3.5 (3.4)	3.5 (3.7)	3.9 (3.4)	4.7 (5.5)
<4 years, %	67	71	60	60
SALT				
Mean (SD)	85 (18)	85 (18)	85 (18)	85 (18)
Severe (SALT 50–94), %	47	49	49	48
EQ-5D-5L				
Baseline health state index	[redacted]	[redacted]	[redacted]	[redacted]
VAS score	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) Skindex–16 AA scores				
Emotions	[redacted]	[redacted]	[redacted]	[redacted]
Functioning	[redacted]	[redacted]	[redacted]	[redacted]
Symptoms	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) HADS total score				
Anxiety	6.1 (4)	6.7 (4)	6.4 (4)	5.9 (4)
Depression	4 (3)	4 (3)	3.8 (3.5)	3.7 (3.5)

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AA, aloecpia areata; EQ-5D, EuroQol-5 dimensions; HADS, Hospital Anxiety and Depression Scale; n, number; SD, standard deviation; SALT, Severity of Alopecia Tool; VAS, visual analogue scale

BRAVE previous treatments

Majority had previous treatment, about half got immunosuppressants normally given for severe disease and some treatments would hardly be given (ciclosporin) or not at all (cryotherapy) in NHS

%	BRAVE-AA1		BRAVE-AA2	
	Baricitinib (n=281)	Placebo (n=189)	Baricitinib (n=234)	Placebo (n=156)
Prior therapy	88	92	90	96
Topical therapy[a]	62	57	63	63
Topical immunotherapy	30	24	27	26
Intralesional therapy	54	53	44	
Systemic agents				
Immunosuppressant	49	53	530)	62
Corticosteroids	37	36	44	49
JAK inhibitor	5	6	4	6
Others	31	30	22	35
Cyclosporin	25	24	12	17
Methotrexate	10	8	13	17
Other systemic non-immunosuppressant	10	9	8	10
Phototherapy	19	12	16	18
Procedures[b]	23	16	20	22

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[a]excludes immunotherapy; [b]cryotherapy, micro-needling, platelet-rich plasma injections; JAK, Janus kinase; n, number

Generalisability of BRAVE population: EAG comments

BRAVE population broadly similar to NHS patients likely to have baricitinib

BRAVE population

- narrower than NICE scope and likely differs from NHS patients having baricitinib because trials excluded people least likely to respond
- has more severe and difficult to treat AA that is more similar to NHS patients with condition than newly diagnosed people with severe AA → may underestimate treatment effect in newly diagnosed population
- had very few permitted concomitant medicines and less than 5% had any for AA

Current AA episode duration and baseline SALT scores can predict treatment response and varies substantially in BRAVE:

- company provided subgroup analyses for severe and very severe AA (SALT 50–95 vs SALT 95–100)
- people with longer episodes of AA, >75 years on lower 2mg dose and people with male pattern baldness have less chance of treatment response
- people disengaged with treatment may reengage to have baricitinib if available

Despite differences, EAG clinical experts consider treatment efficacy likely generalisable to NHS

Are the patients in BRAVE trials generalisable to patients in NHS practice likely to have baricitinib?

AA, alopecia areata; SALT, Severity of Alopecia Tool

BRAVE SALT response rates at week 36

Baricitinib performed better in all SALT outcomes than placebo

Outcome, % (95% CI)	BRAVE-AA1		BRAVE-AA2	
	Baricitinib (n=281)	Placebo (n=189)	Baricitinib (n=234)	Placebo (n=156)
SALT ≤20	35 (30 to 41)	5 (3 to 10)	33 (27 to 39)	3 (1 to 6)
SALT ≤10	[redacted]	[redacted]	[redacted]	[redacted]
$SALT_{50}$	[redacted]	[redacted]	[redacted]	[redacted]
$SALT_{75}$	[redacted]	[redacted]	[redacted]	[redacted]

EAG comments

- At Week 52, [redacted] more people on baricitinib had SALT ≤20 response than at Week 36
- At Week 76, large proportion of people with SALT ≤20 at Week 52 re-randomised to **stay on baricitinib** maintained their response
- At Week 76, large proportion of people with SALT ≤20 at Week 52 re-randomised to **placebo** had lost treatment response
    - Indicates potential long-term efficacy of baricitinib but only if treatment continues
    - Remains uncertain because of lack of comparative placebo data from Week 36 onwards

NICE

CI, confidence interval; N, number; SALT, Severity of Alopecia Tool

BRAVE HRQoL: EQ-5D and HADS

EAG: no meaningful improvement from baseline in EQ-5D or HADS in either arms

EQ-5D-5L	BRAVE-AA1		BRAVE-AA2	
	Baricitinib (n=281)	Placebo (n=189)	Baricitinib (n=234)	Placebo (n=156)
Health state index UK, mean (SD)				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Week 36	[redacted]	[redacted]	[redacted]	[redacted]
VAS, mean (SD)				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Week 36	[redacted]	[redacted]	[redacted]	[redacted]

Week 36	BRAVE-AA1		BRAVE-AA2	
	Baricitinib (n=281)	Placebo (n=189)	Baricitinib (n=234)	Placebo (n=156)
HADS Anxiety				
Mean (SD) baseline score	[redacted]	[redacted]	[redacted]	[redacted]
LSM (SE)	[redacted]	[redacted]	[redacted]	[redacted]
HADS Depression				
Mean (SD) baseline score	[redacted]	[redacted]	[redacted]	[redacted]
LSM (SE)	[redacted]	[redacted]	[redacted]	[redacted]

NICE

*p<0.05 vs placebo; EQ-5D, EuroQol-5 dimensions; HADS, Hospital Anxiety and Depression Scale; LSM, least squares mean; n, number; SD, standard deviation; SE, standard error; VAS, visual analogue scale

BRAVE HRQoL: SF-36 and Skindex-16 AA domain

EAG: no meaningful improvement from baseline in SF-36 in either arms. Large improvement in baricitinib compared to placebo in emotions and functioning domains of Skindex-16 AA measure

SF-36	Physical component score				Mental component score			
	BRAVE-AA1		BRAVE-AA2		BRAVE-AA1		BRAVE-AA2	
	Baricitinib (n=281)	Placebo (n=189)	Baricitinib (n=281)	Placebo (n=189)	Baricitinib (n=281)	Placebo (n=189)	Baricitinib (n=281)	Placebo (n=189)
Baseline mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LSM (SE) at Week 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Skindex-16 AA domain		BRAVE-AA1		BRAVE-AA2	
		Baricitinib (n=171)	Placebo (n=119)	Baricitinib (n=234)	Placebo (n=156)
Emotions	Mean (SD) baseline	[redacted]	[redacted]	[redacted]	[redacted]
	LSM (SE) change	[redacted]	[redacted]	[redacted]	[redacted]
Functioning	Mean (SD) baseline	[redacted]	[redacted]	[redacted]	[redacted]
	LSM (SE) change	[redacted]	[redacted]	[redacted]	[redacted]
Symptoms	Mean (SD) baseline	[redacted]	[redacted]	[redacted]	[redacted]
	LSM (SE) change	[redacted]	[redacted]	[redacted]	[redacted]

What is a clinically meaningful change in Skindex-16 AA measure? Are the changes observed in BRAVE clinically meaningful?

NICE

*p<0.05 vs placebo; AA, alopecia areata; HRQoL, health-related quality of life; LSM, least squares mean; n, number; SF-36, 36-item Short form survey

HRQoL findings: EAG comments

EQ-5D data suitable to inform decision making

- Plausible BRAVE have adequately estimated a small gain in utility after baricitinib at population level
- Recognise that severe AA can have large negative impact on QoL for some patients but may not equate to large changes in EQ-5D score at population level because:
  - In large sample, high-quality BRAVE trials, many severe AA had near-ceiling EQ-5D baseline score
  - Only [redacted] on baricitinib had SALT ≤20 response at Week 36 → any treatment effect at population level on HRQoL diluted by [redacted] whose condition did not respond

EAG clinical experts

- HRQoL benefits may lag treatment response in severe AA as people adjust to changes in appearance
- Baricitinib is not curative; people may have anxiety because baricitinib needs to be taken continuously over a long period to maintain hair regrowth, with missed doses potentially resulting in hair loss

How does HRQoL vary across the presentation and treatment of alopecia areata?
Is baricitinib clinically effective?

AA, alopecia areta; EQ-5D, EuroQol-5 dimensions; HRQoL, health-related quality of life; SALT, Severity of Alopecia Tool

Adverse events

Short-term safety profile of baricitinib compared to placebo is favourable but long-term safety is uncertain. Company did not include adverse events in its economic model

Adverse event, %	BRAVE-AA1		BRAVE-AA2		Pooled extension phase
	Baricitinib (n=280)	Placebo (n=189)	Baricitinib (n=233)	Placebo (n=154)	Baricitinib (n=540)
≥1 Treatment emergent AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deaths	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs stopping treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs stopping study	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adverse event, %	BRAVE-AA1		BRAVE-AA2	
	Baricitinib (n=280)	Placebo (n=189)	Baricitinib (n=233)	Placebo (n=154)
1 TE infection	[redacted]	[redacted]	[redacted]	[redacted]
TE herpes zoster	[redacted]	[redacted]	[redacted]	[redacted]
TE herpes simplex	[redacted]	[redacted]	[redacted]	[redacted]
Major adverse cardiovascular event	[redacted]	[redacted]	[redacted]	[redacted]
Malignancies other than NMSC	[redacted]	[redacted]	[redacted]	[redacted]

AE, adverse event; n, number; NMSC, nonmelanoma skin cancer; TE, treatment emergent

Cost effectiveness

NICE National Institute for Health and Care Excellence

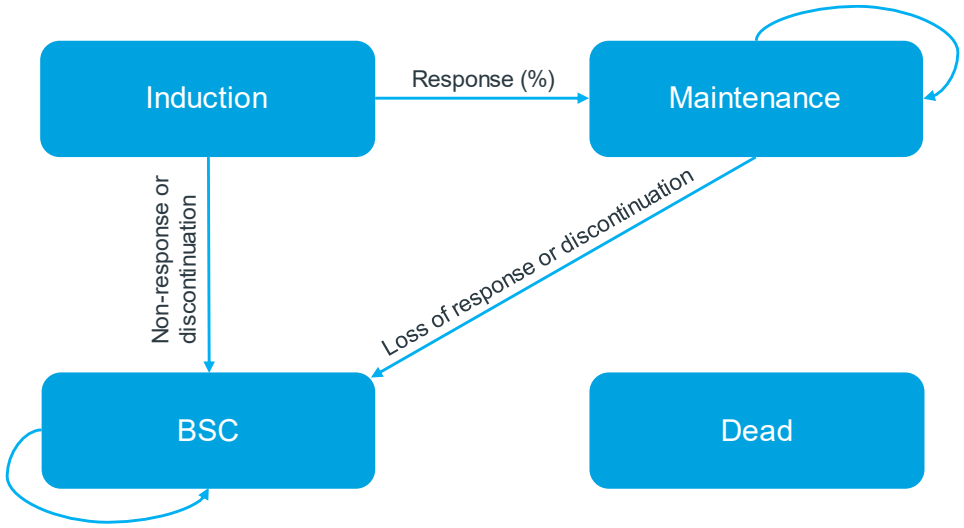
Key cost-effectiveness issues

- Which utilities should be used?
- How should best supportive care be modelled?

Company's model overview

EAG: model structure appropriate; similar to other dermatological conditions e.g. atopic dermatitis

Model structure



- Technology affects **costs** by its higher cost vs established clinical management
- Technology affects **QALYs** by improving and maintaining scalp hair regrowth
- Assumptions with greatest ICER effect:
  - Comparator: removing all monitoring costs in induction and maintenance in 'Watch and Wait'
  - Utilities: using data from BRAVE
  - Best supportive care: removing all costs except for wigs and orthotics

- Cohort Markov 4-health state transition: lifetime horizon, 4-week cycle, no half cycle correction
- UK NHS and PSS perspective, annual discount rate of 3.5% for costs and QALYs
- Induction (36 weeks, 9 tunnel states): baricitinib 4mg vs established clinical management
- Treatment response (based on SALT ≤20 in base case): move to Maintenance or Best supportive care

BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; PSS, Personal Social Services; SALT, Severity of Alopecia Tool

How company incorporated evidence into model (1)

Baseline and efficacy data from pooled BRAVE trials; BSC defined as basket of treatments informed by Adelphi study; company and EAG differ in assumptions on BSC

Input	Assumption and evidence source
Baseline characteristics	Pooled BRAVE trials Base case: age [redacted] years, [redacted] male
Intervention efficacy	Pooled BRAVE phase 3 data: SALT Baricitinib 4mg vs placebo (established clinical management)

Sustained response and treatment stopping	Pooled BRAVE phase 3 data: weeks 0 to 36
	• Base case: all-cause stopping applied on cycle basis
	  ○ Induction: excludes lack of efficacy to avoid double counting
	  ○ Maintenance: baricitinib week 0–52 all-cause stopping rate (updated to 36-52 week); placebo week 0–36 all-cause stopping rate to estimate annual stopping rate
	• Scenario analyses: severe (SALT 50–94), very severe (SALT 95–100)

Best supportive care	• Basket of treatments
	  ○ Base case: composition and proportions from company's Adelphi study
	  ○ Scenario analysis: estimates from 3 UK-based key opinion leaders (KOLs) with current experience of treating severe AA
	  ○ EAG: excluded all treatments except wigs and orthotics

AA, alopecia areata; BSC, best supportive care; SALT, Severity of Alopecia Tool

How company incorporated evidence into model (2)

Company and EAG differ in source of utilities and inclusion of adverse events

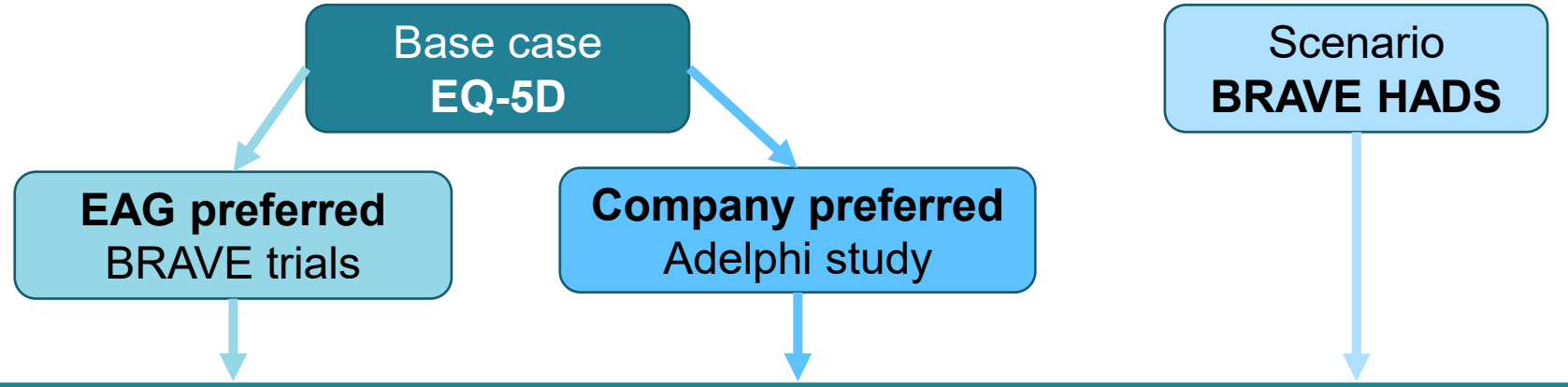
Input	Assumption and evidence source
Utilities	Base case: utilities from EQ-5D-5L data from Adelphi study; age-adjusted based on Health Survey for England (HSE) 2014 dataset ○ EAG: prefers EQ-5D data from BRAVE
Resource use and costs	• Treatment acquisition, monitoring and disease management • Healthcare resource utilisation: Adelphi study and UK clinical expert opinion • National schedule of NHS costs, NHS Drug Tariff, NHS wigs and fabric supports costs and Personal Social Services Research Unit (PSSRU), NICE Guideline on depression in adults (CG90)
Adverse events	• Base case: costs and disutilities associated with AEs excluded ○ Company's justification: AEs mild, little significant detriment in HRQoL or increase in cost ○ EAG: included in scenario analysis
Mortality	• All-cause mortality from Office for National Statistics lifetables between 2017–2019 (to avoid impact of COVID-19 pandemic on data) • Age- and gender-specific rates combined to a blended rate, based on proportion of men and women in model

AE, adverse event; EQ-5D, EuroQol-5 dimensions

Key issue: utilities – data source and dataset

Company uses EQ-5D from Adelphi study in base case; EAG prefers EQ-5D data from BRAVE

UK population norm for people 35-44 years: 0.91



Utilities for full population (SALT 50–100)			
Baseline	[redacted]	[redacted]	[redacted]
CFB SALT ≤20	[redacted]	[redacted]	
CFB SALT$_{50}$	[redacted]	[redacted]	[redacted]
CFB SALT$_{75}$	[redacted]	[redacted]	[redacted]

EAG: some EQ-5D domains relatively unaffected; high baseline scores likely reflect HRQoL in clinical practice
Company has not provided evidence that EQ-5D has poor construct validity and/or responsiveness in severe AA and continues to use EQ-5D albeit from Adelphi study

Company: EQ-5D lacks validity for capturing HRQoL changes in AA

*Company changed figure at clarification; AA, alopecia areata; CFB, change from baseline; EQ-5D, EuroQol-5 dimensions; HADS, Hospital Anxiety and Depression Scale; HRQoL, health-related quality of life

Adelphi study

Company sponsored online survey on mild to severe AA; data from severe or very severe cases from UK setting used in base case

Company

- Company sponsored online survey capturing real-world evidence in October 2021
- [redacted] dermatologists actively treating people with severe/very severe AA in Germany (n=[redacted]), Spain (n=[redacted]), Italy (n=[redacted]), France (n=[redacted]) and UK (n=[redacted]) completed:
  - [redacted] patient record forms for ≥7 consecutive adult patients with mild (n=[redacted]), moderate (n=[redacted]) and severe (n=[redacted]) AA; rating of current severity based on their clinical judgement
  - questionnaires on patient demographics, clinical status, and current treatments
    - Each patient invited to complete self-completion form, including EQ-5D-5L questionnaire
    - Patients excluded if in clinical trial at time of survey
- Base case: current treatments for severe/very severe patients from Adelphi study for UK only (n=117)

EAG comments

- [redacted] severe/very severe AA patients were treatment experienced
  - Treatments primarily given for severe disease e.g. topical immunotherapy, systemic immunosuppressants and systemic steroids
  - However, treatment also given at milder stages e.g. topical corticosteroids

NICE

AA, alopecia areata; EQ-5D, EuroQol-5 dimensions; n, number

BRAVE and Adelphi EQ-5D data

Company: 46% of BRAVE population had perfect EQ-5D score (limit to improvement)

EAG: Adelphi has much smaller sample, high risk of selection and response bias, data not in line with economic model structure

BRAVE: high quality trials; more robust dataset

- N=860 severe/very severe AA
- Data in line with model structure: within-patient change in EQ-5D after SALT ≤20
- 46% had perfect EQ-5D → ceiling effect
- Not representative of UK patients because people with history of anxiety and depression less likely to be recruited (based on clinical expert opinion): [redacted] at screening had significant uncontrolled neuropsychiatric disorders; n=390 needed to reduce baseline EQ-5D from [redacted] to [redacted] (~45% trial size)
- **Other literature:** Adelphi US data 0.89 baseline EQ-5D (n=?/291). ALLEGRO (ritlecitinib for severe AA in adults) EQ-5D-5L did not change from Week 4 to 24

vs

Adelphi: company sponsored; unclear quality (limited data from company for assessment)

- N=[redacted] severe/very severe AA
- Data assumes between-patient difference in EQ-5D of people with different AA severity is equivalent to within-person change in HRQoL when AA severity changes
- 20% had perfect EQ-5D score
- High risk of selection and response bias: dermatologists recruited; patients likely to actively engage with care and chose to complete survey on effects of AA on QoL; answered questions on AA history and symptoms before EQ-5D measure
- **Other literature:** Adelphi Japanese data 0.79 baseline EQ-5D (n=85)

N

AA, alopecia areata; EQ-5D, EuroQol-5 dimensions; n, number; SALT, Severity of Alopecia Tool

Utilities: EAG comments

Small heterogenous population may be more adversely affected but at population level may not result in large HRQoL changes overall

EAG comments

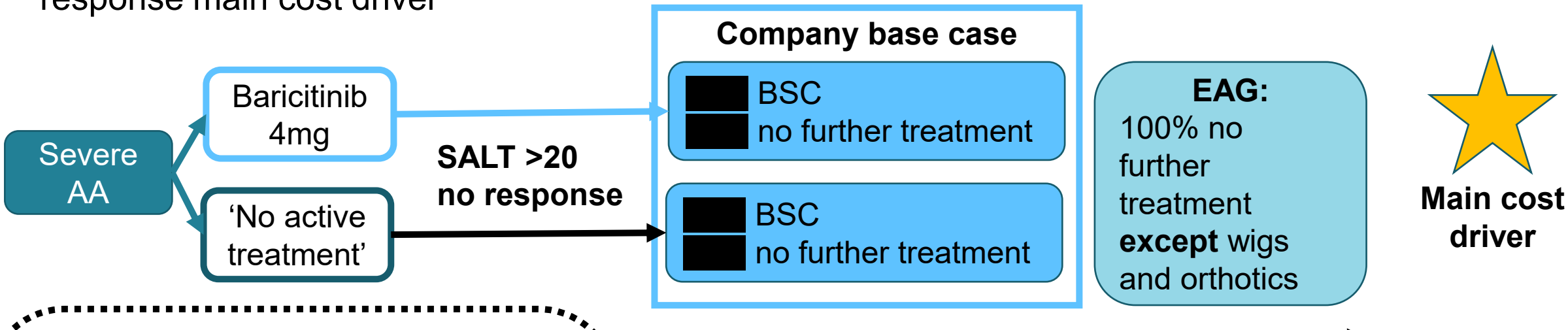
- Prefers to use BRAVE EQ-5D data from people with SALT ≤20 (endpoint used in model)
- Acknowledges small but heterogenous population that is more adversely affected in terms of HRQoL
  - Demographics difficult to identify clinically and consistently; beyond scope of assessment to identify this group
  - At population level, may not lead to large HRQoL gains after baricitinib because:
    - few had SALT ≤20
    - many have high baseline EQ-5D scores
    - baricitinib is not curative
    - hair regrowth may not lead to greatly improved HRQoL, if other sources of reduced HRQoL, e.g. depression and/or anxiety, are not directly treated
- Estimated QALY gain needed to reach £20,000 and £30,000 cost-effectiveness thresholds
  - Committee to consider if estimated QALY gain needed for baricitinib is plausible for severe AA

Which data source should inform utilities in model? BRAVE trials or Adelphi study?
Which dataset should inform utilities in model? EQ-5D or HADS?

AA, alopecia areata; EQ-5D, EuroQol-5 dimensions; HADS, Hospital Anxiety and Depression Scale; HRQoL, health-related quality of life; QALY, quality-adjusted life year; SALT, Severity of Alopecia Tool

Key issue: best supportive care – composition and usage

Assumptions about composition of BSC and proportion of people having BSC after no treatment response main cost driver



BSC basket

Treatment	Percentage of use	
	Adelphi	3 UK KOLs
Ciclosporin	14%*	13%
Methotrexate	13%*	8%
Azathioprine	3%	9%
Intralesional steroids	9%*	31%
DPCP (contact immunotherapy)	22%*	28%
Prednisolone	17%	25%
Topical corticosteroids	25%	63%
Minoxidil 5% foam (topical)	6%	38%
Minoxidil tablets	0%	8%
Mycophenolate mofetil	3%	0%
Anthralin 0.1% cream	6%	0%
Patients not on treatment	[redacted]	**0%**
Wig use (modacrylic wig)	NA	80%

*Updated at clarification

BSC costs
- Annual drug acquisition
- Drug monitoring
- Disease management

'BSC' costs
- Wigs and orthotics

AA, alopecia areata; BSC, best supportive care; DPCP, 2,3-diphenylcyclopropenone; KOL, key opinion leads; n, number

Best supportive care composition and usage assumptions

Company: BSC includes basket of treatments; differential BSC usage for baricitinib and 'no active treatment'. EAG: BSC includes only wigs and orthotics; usage same for baricitinib and 'no active treatment'

EAG

- Adelphi: [redacted] treatment experienced
- If non-response: unlikely to engage in further treatment (if all options exhausted) or discharged from care
  - Clinically implausible for limited effective treatments to be given for lifetime horizon
  - Many may choose camouflage options
- **Base case for both arms:** exclude drug acquisition and monitoring costs and disease management. **Keep wigs and orthotics**
- **Scenario analyses for both arms:** BSC use at 25% and 50%

Company

- If non-response, unlikely everyone will have no further treatment and be discharged from care
- Prescribers may be less willing to prescribe BSC treatments after treatment failure with baricitinib
- Differential BSC usage
  - Baricitinib: relative reduction to 'no active treatment' → incurs lower BSC costs
- **BSC: basket of treatment**
- **Base case BSC usage:** [redacted] 'no active treatment' vs [redacted] baricitinib
- **Scenario analyses:** range of BSC usage in 'no active treatment' (10–100%), with baricitinib relative reduction range (25–100%)

What comprises BSC for people with severe AA after all possible treatment options have been exhausted? What proportion of people with severe AA would continue to have BSC after all possible treatment options have been exhausted? Would proportions be different depending on the last line of treatment, that is, baricitinib or no active treatment?

Summary of company and EAG base case assumptions

Assumption	Company original base case	Company revised base case after technical engagement	EAG base case
Comparator 'Watch and Wait'	Monitoring costs in induction and maintenance	Removed monitoring costs	No monitoring costs in induction and maintenance
Treatment response at Week 36	$SALT_{50}$	SALT ≤20	SALT ≤20
Utilities	**Adelphi study**	**Adelphi study**	**BRAVE**
Long-term all-cause stopping	Week 0 to 52 data for baricitinib [redacted]	Week 36–52 data for baricitinib ([redacted])	Week 36–52 data for baricitinib ([redacted])
Best supportive care (BSC)	**Both arms: [redacted] have BSC after no treatment response**	**Baricitinib: [redacted]** **'No active treatment': [redacted]**	**Both arms: wigs and orthotics only**
Non-pharmacological psychological support costs	Included	Excluded	Excluded
Wig use (induction only)	2 in both arms	1 in both arms	1 in both arms

SALT, Severity of Alopecia Tool

Company revised base case results

BSC drugs commissioned in **primary care**, PAS price

Deterministic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB (£20k /QALY)	NHB (£30k /QALY)
No active treatment ('Watch and Wait', no monitoring)	[redacted]	[redacted]					
Baricitinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]

Probabilistic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB (£20k /QALY)	NHB (£30k /QALY)
No active treatment ('Watch and Wait', no monitoring)	[redacted]	[redacted]					
Baricitinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]

BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; NHB, net health benefit; PAS, Patient Access Scheme

Company deterministic scenario analysis

BSC drugs commissioned in **primary care**, PAS price

No.	Scenarios (applied to company revised base case)	Inc costs (£) vs no active treatment	Inc QALYs vs no active treatment	ICER (£) vs no active treatment
1	**Company revised base case**	[redacted]	[redacted]	Dominant
2	Response $SALT_{75}$	[redacted]	[redacted]	Dominant
3	Response $SALT_{50}$	[redacted]	[redacted]	Dominant
4	Response SALT ≤10	[redacted]	[redacted]	Dominant
5	Utilities: pooled EQ-5D data from BRAVE	[redacted]	[redacted]	Dominant
6	Utilities: pooled HADS data from BRAVE	[redacted]	[redacted]	Dominant
7	Response SALT ≤20 – severe (SALT 50–94)	[redacted]	[redacted]	Dominant
8	Response SALT ≤20 – very severe (SALT 95–100)	[redacted]	[redacted]	Dominant
9	Response SALT ≤20 & duration of AA episode <4 years	[redacted]	[redacted]	Dominant
10	Response SALT ≤20 & duration of AA episode >4 years	[redacted]	[redacted]	Dominant
11	Wig costs weighted by proportion of females (61%)	[redacted]	[redacted]	Dominant

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AA, alopecia areata; BSC, best supportive care; EQ-5D, EuroQol-5 dimensions; HADS, Hospital Anxiety and Depression Scale; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; QALY, quality-adjusted life year; SALT, Severity of Alopecia Tool

EAG deterministic scenario analysis using company revised base case

BSC drugs commissioned in **primary care**, PAS price

No.	Scenarios (applied to company revised base case)	Inc costs (£) vs no active treatment	Inc QALYs vs no active treatment	ICER (£) vs no active treatment
1	**Company revised base case**	[redacted]	[redacted]	Dominant
2	Proportion receiving BSC in both arms - 0% (EAG preferred assumption)	[redacted]	[redacted]	61,056
3	Proportion receiving BSC in both arms - 25%	[redacted]	[redacted]	51,575
4	Proportion receiving BSC in both arms - 50%	[redacted]	[redacted]	42,095
5	Inclusion of adverse event costs	[redacted]	[redacted]	Dominant
6	SALT ≤20 baseline and utilities from BRAVE	[redacted]	[redacted]	Dominant

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BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; QALY, quality-adjusted life year; SALT, Severity of Alopecia Tool

EAG preferred assumptions: base case and scenario analysis

BSC drugs commissioned in **primary** care, PAS price

No.	Scenarios (applied to company revised base case)	Inc costs (£) vs no active treatment	Inc QALYs vs no active treatment	ICER (£) vs no active treatment	Cumulative ICER
1	**Company revised base case**	[redacted]	[redacted]	Dominant	-
2	SALT ≤20 baseline and utilities from BRAVE	[redacted]	[redacted]	Dominant	Dominant
3	Proportion receiving BSC in both arms - 0%	[redacted]	[redacted]	61,056	423,803
4	Inclusion of adverse event costs	[redacted]	[redacted]	Dominant	425,560
5a	**EAG base case (deterministic)**	[redacted]	[redacted]	**425,560**	-
5b	**EAG base case (probabilistic)**	[redacted]	[redacted]	**462,142**	-
6*	Response SALT ≤20 – severe (SALT 50–94)	[redacted]	[redacted]	408,979	-
7*	Response SALT ≤20 – very severe (SALT 95–100)	[redacted]	[redacted]	458,392	-

*Same baseline utility ([redacted]), change from baseline ([redacted]) and treatment stopping rate ([redacted]) from base case because relevant data not available by severity

BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; QALY, quality-adjusted life year; SALT, Severity of Alopecia Tool

EAG threshold analysis on QALY gain needed

No.	Population	QALY gain - £20,000 threshold	QALY gain - £30,000 threshold
1	**Baseline SALT 50–100**	[redacted]	[redacted]
2	Severe subgroup - baseline SALT 50–94	[redacted]	[redacted]
3	Very severe subgroup - baseline SALT 95–100	[redacted]	[redacted]

QALY, quality-adjusted life year; SALT, Severity of Alopecia Tool

Part 2

ICERs including Commercial Medicine Unit prices are reported in PART 2 slides because they include confidential discounts for drugs in best supportive care that are assumed to be prescribed mainly in secondary care

Other considerations

Equality considerations

- Some cultures loss of beard hair can be an important issue

Innovation

- Step change in management of severe AA: first licensed treatment
- Difficulty in capturing psychosocial impact in EQ-5D measures

Is baricitinib innovative?
Are there any equality issues to consider?

AA, alopecia areata; EQ-5D, EuroQol-5 dimensions

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Thank you