Single Technology Appraisal

Ritlecitinib for treating severe alopecia areata in people 12 years and over [ID4007]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ritlecitinib for treating severe alopecia areata in people 12 years and over [ID4007]

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from Pfizer**

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. Alopecia UK
   b. British Association of Dermatologists

3. **Comments on the Draft Guidance Document from experts:**
   a. Lynn Wilks – patient expert, nominated by Alopecia UK (**see item 2a)*
   b. Nekma Meah – clinical expert, nominated by the British Association of Dermatologists

4. **Comments on the Draft Guidance received through the NICE website**

5. **External Assessment Group critique of company responses**
   a. to additional evidence request
   b. to draft guidance response

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

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Pfizer Ltd

Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Submitting company
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted], Pfizer Ltd.

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
0	**Executive summary** The company welcomes the opportunity to comment on the draft Appraisal Consultation Document (ACD) which recognises ritlecitinib as a clinically effective, innovative medicine and that janus kinase (JAK) inhibitors provide a new mechanism of action for treating severe alopecia areata. The company also welcomes the committee position that, to account for uncaptured benefits and the innovative nature of ritlecitinib, an acceptable incremental cost effectiveness ratio (ICER) for ritlecitinib in treating severe alopecia areata in people 12 years and over would be towards the top of the range usually considered a cost-effective use of NHS resources. However, the company are disappointed that despite providing evidence aligned to the committee's preferred assumptions along with an adjustment in price to reach an ICER of £25,626-£29,988 per quality adjusted life year (QALY), ritlecitinib was still not recommended following the first appraisal committee meeting (Comment 1).

	The company continue to offer the enhanced patient access scheme (PAS) [redacted] to align to the committee preferred assumptions, but we maintain that these assumptions are highly conservative. The updated PAS demonstrates the companies continued commitment to providing a new treatment to the UK alopecia areata (AA) community where no reimbursed systemic treatment currently exists. With the updated PAS, the committee preferred base-case is cost-effective, and company base case highly cost effective. The company have taken the opportunity to present further new evidence in our ACD response to address the committees queries and concerns. The following key points summarise the additional data presented. • AA has a significant impact on patients' health related quality of life (HRQoL) that is not fully captured by EQ-5D or other generic measures of HRQoL and there are currently no condition specific preference-based measures that are suitable. • The committee have concluded that severe AA has wide ranging effects and can have a profound impact on quality of life and accepts the limitations of the generic HRQoL results from the ALLEGRO 2b/3 trial. The EAG agreed that using EQ-5D from the ALLEGRO 2b/3 is unlikely to capture the severity of the condition and is unlikely to be appropriate as there may be some underestimation of QALY gains. Any estimates of cost effectiveness based on utility estimates from the trial are inconsistent as it assumes AA has no impact on patients. Any scenario being considered by the committee that lacks external validity and we encourage the committee to consider this (Comment 2). • New evidence from the ALLEGRO LT study (requested by the committee) shows no change in EQ-5D across categorical severity of alopecia tool (SALT) states over time which do not reflect patient and clinician and external assessment group (EAG), or the committee's conclusions. The trial-based utilities are not an appropriate source of health-state utility values (Comment 2). • The committee have requested evidence of a lack of sensitivity or responsiveness to EQ-5D based on synthesis of data from the literature. The companies evidence synthesis (SLR, Appendix H. company submission, targeted literature search, Appendix A) did not identify any longitudinal data reporting EQ-5D over time, or any clinical trials reporting EQ-5D changes in response to treatment other than ritlecitinib. The EAG acknowledge the difficulties in assessing content validity or responsiveness in a disease with such paucity of data and few effective treatments.

	Any assessment of responsiveness is therefore limited to the outcomes reported in the ALLEGRO studies (Doc B.1.3.2.3 and B.3.4.1) (Comment 3). • New evidence presented by the company assesses the construct validity and responsiveness of the EQ-5D and SF-36 through a post hoc analysis of the ALLEGRO-2b/3 trial data. Results show that generic preference-based instruments, EQ-5D and SF-36, administered in the trial, demonstrated issues with construct and content validity, and responsiveness, with substantial observed ceiling effects across known patient groups. EQ-5D and SF-36 are not valid measures of HRQOL in alopecia areata (Comment 3). • The new evidence presented supplements the qualitative analysis included in the company submission based on clinician and patient feedback (Doc B.3.4.4.2) which showed that EQ-5D is too broad and does not capture all the lived impacts faced by patients with AA in a meaningful way. These results are consistent with the feedback at the first appraisal committee and as reported in TA926.[1] (Comment 3) • No condition-specific preference-based utility measures exist for AA. Whilst DLQI has been mentioned as a potential option this measure is also unsuitable due to concerns over content validity and relevance to AA (Comment 5). • Based on the evidence summarised above, the committee-preferred utility estimate source (Bewley et al.) based on EQ-5D is unable to characterise the entire HRQoL burden for patients living with AA (Comment 6). • The company vignette TTO results are representative of the HRQoL burden for patients with AA. The company provides two additional sources of evidence both of which reinforce the validity of the utility estimates generated from the vignettes TTO in the general population (Comment 4). - A non-interventional, cross-sectional extension of the original vignette TTO study to estimate the utilities for health states describing AA using TTO interviews with patients with AA. The results show comparable utility estimates to the original vignette TTO in the general population and confirm the internal validity of the original vignette TTO. - A multi-component scoping review study to collate and describe utility values for a proxy condition, which is conceptually similar to AA in terms of patients lived experience and HRQoL (atopic dermatitis). Utility estimates for AD overlap with the utility estimates from the original vignette TTO

validating the plausibility of the vignette TTO results and confirm the external validity of the original vignette TTO.

In addition, a number of the committee's preferred assumptions are conservative and result in a reduction in the committee preferred ICER and should be taken into consideration in decision making (Table 1).

- Proportion of patients in the model who are adolescent, reflecting the generalisability to the UK clinical context based on clinical opinion (Comment 8).

- Best supportive care defined as only non-pharmacological treatment options is conservative based on TA681 and clinical opinion (Comment 7).[1, 2]

- The committee preferred assumptions resulting in an average time on treatment of less than 3 years is inconsistent with the ALLEGRO-LT clinical data. (Comment 9)

- The committees preferred utility source Bewley et al. has been published in full (Vañó-Galván et al.) resulting in a reduction of the committee preferred ICER to £28,367 /QALY.[3]

In conclusion, utilities generated from EQ-5D or SF-36 from the ALLEGRO 2b/3 trial, and ALLEGRO LT, along with those from the literature remain inappropriate to characterise the full burden of AA to patients. This has been recognised by the EAG, patient and clinical experts and acknowledged in the conclusions of the committee. The new psychometric analysis of EQ-5D and SF-36 provides further evidence these measures do not capture the full burden of AA and therefore calls into question any source of utilities derived from EQ-5D and SF-36 in the literature including the committee preferred utility source (Bewley et al.). Any assessment of cost-effectiveness based on these estimates will underestimate the full benefits of treatment with ritlecitinib in patients with AA and is therefore highly conservative. In addition, condition specific preference based derived utilities for AA either do not currently exist or in the case of DLQI are unsuitable. Utility estimates derived from the original vignette TTO exercise accurately capture the HRQoL impact as described by patients and clinicians. These values have been validated by two additional sources of evidence provided by the company, the vignette TTO in the AA population and conceptual overlap analysis.

Despite these conclusions, the company have provided an increased PAS, resulting in a cost-effective committee preferred base-case and highly cost effective company base-case. The resulting ICERs of these two analyses along with other scenario provided by the company in response to the ACD are summarised in Table 1.

Table 1: Summary of the ICERs presented in the ACD response.

Scenario	Total BSC costs (£)	Total BSC QALYs	Incremental costs of ritlecitinib (£)	Incremental QALYs of ritlecitinib	ICER of ritlecitinib compared to BSC (£)
Committee Scenarios					
Committee unweighted base case (using Bewley abstract)	[redacted]	[redacted]	[redacted]	[redacted]	28,633
Committee weighted by AT/AU prevalence (UK)	[redacted]	[redacted]	[redacted]	[redacted]	25,626
Committee weighted by adolescent prevalence (UK) 4.91% adolescents	[redacted]	[redacted]	[redacted]	[redacted]	29,988
Committee unweighted base case (using Bewley manuscript)	[redacted]	[redacted]	[redacted]	[redacted]	28,367
Committee unweighted, time on treatment ([redacted] yrs): Stay in state, Weibull	[redacted]	[redacted]	[redacted]	[redacted]	23,914
Committee unweighted, time on treatment ([redacted] yrs): Stay in state, exponential	[redacted]	[redacted]	[redacted]	[redacted]	24,022
Committee weighted, time on treatment ([redacted] yrs): Stay in state, gen gamma	[redacted]	[redacted]	[redacted]	[redacted]	24,615

	Committee weighted, time on treatment ([redacted] yrs): Stay in state, gompertz	[redacted]	[redacted]	[redacted]	[redacted]	25,172
	Company Scenarios					
	Company base case	[redacted]	[redacted]	[redacted]	[redacted]	8,294
	Company base case using vignette TTO of patients with AA	[redacted]	[redacted]	[redacted]	[redacted]	7,767
	Company base case using AD utilities	[redacted]	[redacted]	[redacted]	[redacted]	17,973
	Company base case with pharmacological treatment costs for BSC	[redacted]	[redacted]	[redacted]	[redacted]	74 to 6,743
	Company base case - adults	[redacted]	[redacted]	[redacted]	[redacted]	8,940
	Company base case - adolescents	[redacted]	[redacted]	[redacted]	[redacted]	7,986
	Company base case – with carers for adults	[redacted]	[redacted]	[redacted]	[redacted]	7,685
1	**The company has provided an updated PAS (reduced price) with all of the committee's preferred assumptions and demonstrated ritlecitinib as a cost-effective use of NHS resources.** The committee have acknowledged that severe AA has wide ranging effects and can have a profound impact on quality of life with no standard of care and inequitable access to limited treatment options. The company are concerned that, despite the evidence submitted aligning to the committee's preferred assumptions along with a revised PAS following the					

	first appraisal meeting, the committee have not recommended ritlecitinib for the treatment of severe AA in adults and adolescents 12 years of age and older. • To account for uncaptured benefits and the innovative nature of ritlecitinib, the committee agreed that an acceptable ICER for ritlecitinib for treating severe alopecia areata in people 12 years and over would be towards the top of the range usually considered a cost-effective use of NHS resources. • The company proposed that the price of ritlecitinib was reduced to reach an ICER of £25,626-£29,988/QALY while using all of the committee's preferred assumptions, including weighting the ICER according to whether patients had AT/AU and by age as indicated by the committee. The company believes these assumptions remain conservative with several scenarios reduce the ICER in the committee base case: - Proportion of patients in the model who are adolescent, generalisability of findings to the UK – In the ACD, it is reported that the clinical experts advised that '*the proportion of young people included in the ALLEGRO trials underrepresented the proportion seen in clinical practice*'. Since the ICER is lower for adolescents than adults any increase above the proportions reported in the ALLEGRO 2b/3 trial and included in the model will result in ICERs that are below the current company base case. - Best Supportive Care - Only including non-pharmacological treatment options in the best supportive care health states is conservative to ritlecitinib and should be taken into consideration. Using the same assumptions as accepted by the committee in TA681, the ICERs when including the pharmacological treatment costs of BSC are less than the ICER when not including pharmacological treatment costs of BSC, showing that not including pharmacological treatment costs of BSC is conservative. - Average time on treatment of less than 3 years is conservative – the committee's preferred assumption on treatment waning effect and discontinuation results in a low average time on treatment. Evidence from ALLEGRO LT over 24 months show that patients who are responding remain on treatment i.e. no waning effect of treatment. The company have explored their own clinical opinion which reinforces that AA is a chronic condition and patients will remain on treatment long term.[2] The company argues therefore that broader clinical opinion points to the longer term use of ritlecitinib as a chronic treatment and therefore uncertain as acknowledged by the committee. The

	assumption of average of transitions and exponential discontinuation is therefore a conservative assumption. - The committees preferred utility source Bewley et al. has been published in full (Vañó-Galván et al.) resulting in a reduction of the ICER to £28,367 /QALY.[3] In consideration of the committee's preferred assumptions and the agreement an acceptable ICER would be towards the top of the range, the ICER for ritlecitinib using the updated price for ritlecitinib provided comfortably falls within the willingness-to-pay threshold. The statement that "given that the cost-effectiveness estimates preferred by the committee were not within the range usually considered a cost-effective use of NHS resources, including those for the subgroup of young people aged 12 to 17 years" is therefore incorrect.
2	**EQ-5D and SF-36 data from the ALLEGRO 2b/3 and ALLEGRO-LT trials are inconsistent with the burden of the condition as described by patients, clinicians and as described in the literature. The trials are therefore not a valid source of utilities.** The company maintains that utility estimates derived from the ALLEGRO 2b/3 and LT clinical studies are inconsistent with the burden of AA as described by patients, clinicians, and reinforced in the literature. [4-6] The committee have also concluded that *severe alopecia areata has wide ranging effects and can have a profound impact on quality of life.* The ACD notes that *the patient and clinical experts agreed that EQ-5D data from the ALLEGRO 2b/3 trial is unlikely to capture the severity of the condition.* The EAG agreed that *using the EQ-5D results from ALLEGRO 2b/3 was unlikely to be appropriate, because of selection bias, high baseline scores and the short follow-up period of the trial.* As a result, the EAG state *there may be some underestimation of QALY gains when using EQ-5D based utility estimates obtained directly from ALLEGRO-2b/3* and therefore unlikely to be appropriate (EAG report and comments in the first appraisal committee meeting (ACM). The committee goes on to accept *the limitations of the EQ-5D results from the ALLEGRO 2b/3 trial* (Section 3.13, ACD). The company believes any estimates of cost effectiveness based on utility estimates from the trial are inconsistent, lacking external validity and we encourage the committee to consider this.

	Long term EQ-5D data from ALLEGRO-LT are consistent with ALLEGRO 2b/3 and suggests utility estimates do not change over time and are therefore also not a valid source of utility estimates. EQ-5D at baseline, Week 24, and Week 48 of the ALLEGRO 2b/3 study were presented in the company submission (Doc B.3.4.1). These results demonstrated high baseline utilities with very little change over the duration of the study. Due to the high baseline utility values, there is a ceiling effect in the improvements in EQ-5D that may be demonstrated during treatment. As highlighted by the EAG and subsequently requested by the committee, EQ-5D presented from the longer term ongoing ALLEGRO-LT study *"might help inform the suitability of EQ-5D for estimating health-related quality of life in this population"* (section 3.13, ACD). To address this, ALLEGRO-LT EQ-5D-5L data is presented in Figure 1 and Figure 2 and has been converted to EQ-5D-3L and valued using the UK tariff using the Hernandez-Alava crosswalk, in line with NICE guidance.[1] Results show participants who received study intervention in ALLEGRO 2b/3 (who completed EQ-5D-5L questionnaires) and rolled over to the ALLEGRO-LT study, where baseline refers to the baseline of the original study (i.e., from ALLEGRO 2b/3). At baseline, the mean (standard error) utility value in roll-over patients was [redacted]. After 24 months in the ALLEGRO-LT study (equal to approximately 30-36 months on ritlecitinib 50mg), the mean utility value was [redacted]. In roll-over patients, the mean utility value remained stable across time in the study and is consistent across categorical SALT based health states.

Figure 1: EQ-5D utility values over time in roll-over 50mg ALLEGRO LT patients.

SALT, Severity of Alopecia Tool; QD, once daily.
n/N indicated for each timepoint; N: Number of patients with observed data; n: Number of patients with recorded EQ-5D. Confidence interval for percentages is based on normal approximation.
*Includes all patients who rolled over into ALLEGRO LT from ALLEGRO 2b/3
EQ-5D-5L mapping algorithm code (STATA/R packages) EEPRU paper.[7]

Figure 2: EQ-5D utility values over time by SALT state in roll-over 50mg ALLEGRO LT.

SALT, Severity of Alopecia Tool; QD, once daily.
n/N indicated for each timepoint; N: Number of patients with observed data; n: Number of patients with recorded EQ-5D. Confidence interval for percentages is based on normal approximation.
*Includes all patients who rolled over into ALLEGRO LT from ALLEGRO 2b/3
EQ-5D-5L mapping algorithm code (STATA/R packages) EEPRU paper.[7]

Results are presented in Figure 3 and Figure 4 from the modified *de novo* group who joined the ALLEGRO-LT study, where baseline refers to the baseline of ALLEGRO-LT study (i.e., the initiation of their treatment with ritlecitinib). The modified *de novo* cohort is presented as this is aligned with the anticipated licensed indication of ritlecitinib, i.e., patients must have had a SALT score of ≥50 at baseline. At baseline of the ALLEGRO-LT study, the mean (standard error) utility value in modified *de novo* patients were [redacted]. After 24 months in the ALLEGRO-LT study, the mean utility value was [redacted]. In the modified *de novo* patients, the mean utility value remained stable across time in the study, and this is consistent across categorical SALT based health states.

Figure 3: EQ-5D utility values over time in modified *de novo* ALLEGRO-LT patients

SALT, Severity of Alopecia Tool; QD, once daily.
n/N indicated for each timepoint; N: Number of patients with observed data; n: Number of patients achieving SALT score ≤20. Confidence interval for percentages is based on normal approximation.
Includes all new patients in ALLEGRO-LT (modified de novo, MDM) from the start of their first dose of ritlecitinib.
EQ-5D-5L mapping algorithm code (STATA/R packages) EEPRU paper.[7]

Figure 4: EQ-5D utility values over time by SALT state in modified *de novo* ALLEGRO-LT patients.

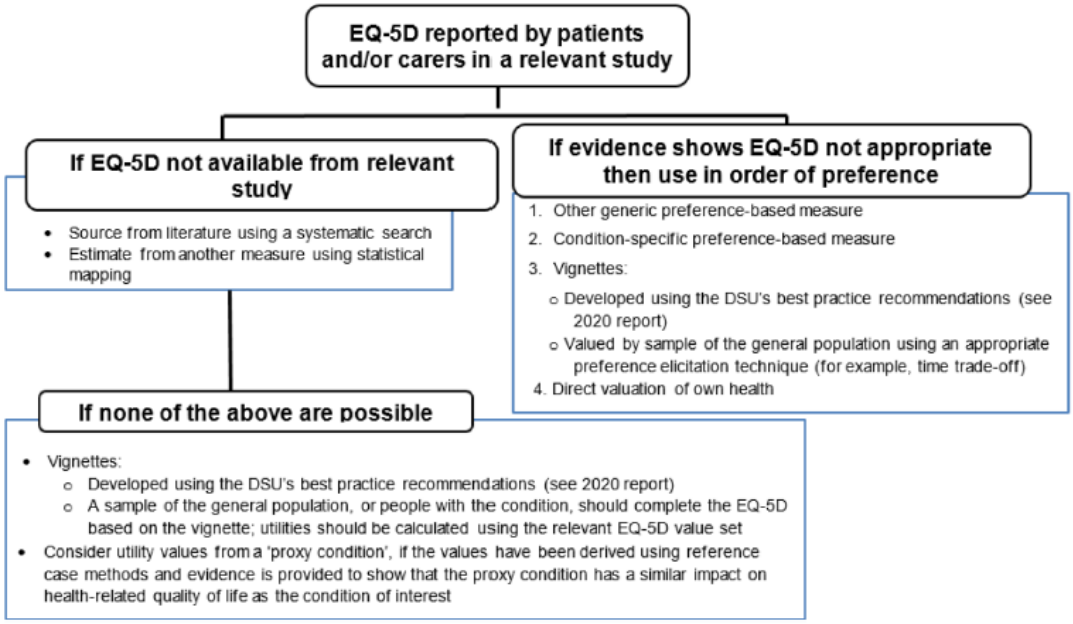
SALT, Severity of Alopecia Tool; QD, once daily; mDN, modified de novo
n/N indicated for each timepoint; N: Number of patients with observed data; n: Number of patients achieving SALT score ≤20. Confidence interval for percentages is based on normal approximation.
Includes all new patients in ALLEGRO-LT (modified de novo, mDN) from the start of their first dose of ritlecitinib.
EQ-5D-5L mapping algorithm code (STATA/R packages) EEPRU paper.[7]

Considering both the roll-over and modified *de novo* patients of the ALLEGRO-LT study, the health state utility values remain consistent regardless of time on treatment with ritlecitinib. Low variability in the EQ-5D values over time suggests homogeneity and no subgroups, including as presented those defined by SALT scores, with substantially different mean EQ-5D values.

The results from the ALLEGRO-LT study are consistent with the results from ALLEGRO 2b/3; across all patients, there is a very high baseline utility value which does not show signs of change with extended ritlecitinib treatment. Moreover, the baseline utility values in the

	modified *de novo* group are consistent with those observed at baseline in ALLEGRO 2b/3; both groups have very high baseline utility values predicating a ceiling effect for the potential improvement in EQ-5D with improvement in SALT score. The data from the ALLEGRO 2b/3 and ALLEGRO-LT study support the conclusion reached by the company that the trial-based utilities are not an appropriate source of health-state utility values. In addition, the data does not support the suggestion by the EAG that the follow up may have been too short to have detected a change in quality of life. Patients did not worsen from baseline, their HRQoL remained unchanged throughout the trial period extending into the long term by up to 36 months. Therefore, EQ-5D data from the ALLEGRO 2b/3 and LT studies should bear no consideration in decision making. This conclusion was supported by the EAG who noted that "*there may be some underestimation of QALY gains when using EQ-5D based utility estimates obtained directly from ALLEGRO-2b/3*". In response to the committee question at the ACM, the EAG reaffirmed this position. Furthermore, a psychometric analysis of ALLEGRO 2b/3 outlined in comment 3 supports the unsuitability of generic measures as a source of utility estimates. Therefore, a scenario where health state utility values are informed by the longest available EQ-5D data from the ALLEGRO trials has not been provided. However, in response to the committee request the mean utility estimates by health state from ALLEGRO 2b/3 and ALLEGRO LT (the longest available timepoint) are provided in Appendix B.
3	**A synthesis of peer-reviewed literature along with a targeted literature search found no evidence of the evaluation of sensitivity and/or responsiveness of EQ-5D or SF-36. The company has provided new psychometric evidence, as suggested by the EAG, that EQ-5D performs poorly on tests of content validity and responsiveness based on an analysis of EQ-5D and SF-36 from ALLEGRO 2b/3.** Demonstrating that the EQ-5D is insensitive to the effects of a specific disease can involve a combination of qualitative and quantitative research. The NICE methods guide states that to make the case that the EQ-5D is inappropriate, evidence should be provided on the content validity, construct validity and responsiveness of the EQ-5D in the population of interest as outlined in Figure 5.[8]

Figure 5: Hierarchy of preferred health-related quality of life methods



NICE health technology evaluations: the manual.[8]

The EAG have acknowledged that *"it may be difficult to assess responsiveness in a disease with few effective treatments unless a prospective study exists following patients over time"* (Page 131, EAG report). There is a paucity of data on the HRQoL impact for patients with AA. The company's HRQoL SLR (Appendix H of the Company submission) did not identify any longitudinal data reporting EQ-5D over time, or any clinical trials reporting EQ-5D changes in response to treatment for treatments other than ritlecitinib. In addition, the targeted literature search on utility values in AA as part of the vignette TTO study development (Appendix A), also provides no evidence on the content validity or responsiveness of EQ-5D in this population. Any assessment of responsiveness is therefore limited to the outcomes reported in the ALLEGRO studies.

Therefore, in addition to the quantitative assessment of EQ-5D responsiveness and unsuitability alongside other generic utility sources (Doc B.3.4.1.1 and B.3.4.4.2), the company has conducted a psychometric analysis of the ALLEGRO 2b/3 data, the company believes this is the first of such (within trial) assessments in AA. The data presented provides evidence that EQ-5D (and SF-36) are unsuitable and, in addition, reinforces the company opinion that EQ-5D (and SF-36), outside of a clinical trial setting, captures some, but not all, of the burden of AA. Therefore any cost-effectiveness analysis that uses EQ-5D or SF-36 to generate utility scores results in a significant underestimation of the incremental QALYs associated with treatment. Further detail on the quantitative assessment of the ALLEGRO 2b/3 data along

with a summary of relevant qualitative analysis provided previously by the company is outlined below.

1. **Construct validity and responsiveness – Psychometric Analysis of ALLEGRO 2b/3.[9]**

To assess construct validity and responsiveness the company has conducted a post hoc analysis of the ALLEGRO 2b/3 trial data to evaluate the performance of the EQ-5D and SF-36. EQ-5D-5L responses were crosswalked to EQ-5D-3L index scores using the DSU recommended Hernandez-Alava et al. UK crosswalk algorithm.[7] Several measurement properties were characterised:

- **Ceiling effects**: high ceiling effects in the EQ-5D-5L were observed where large proportions of patients reported no problems in all five dimensions across several patients groups, including by SALT categories ([redacted]) and by PGI-C response ([redacted]) scores.

- **Construct validity**: in the exploratory factor analysis which included EQ-5D, SF-36 and the validated alopecia areata patient priority outcomes (AAPPO) scales[10], nine factors emerged explaining [redacted]% of the variance of all responses on every item across all instruments, following orthogonal rotation. These factors are likely related to themes of emotional and social functioning, physical functioning, general health, extent of hair loss, emotional symptoms relating to hair loss, activity limitations relating to hair loss, pain, daily activities/self-care and physical impairment impacting activities. Three factors emerged which described concerns resulting from hair loss which included AAPPO items but not EQ-5D. This suggests that the AAPPO is capturing distinct HRQoL impacts not captured by the EQ-5D or SF-36.

- **Known-groups evidence:** The EQ-5D and SF-36 physical and mental component scores did not differentiate between subgroups of participants defined by SALT scores or treatment response defined by patient global impression of change (PGI-C) at either Week 24 or Week 48. This does not align to the described burden by patients.

- **Responsiveness**: Patterns of correlations for participants were significant, but generally weak. Weak correlations of change from baseline to Week 24 and Week 48 for EQ-5D and SF-36 scores with changes in SALT scores (|r| [redacted], PGI-C scores (|r| [redacted], and changes in AAPPO emotional symptoms (|r| [redacted] and activity limitations subscales (|r| [redacted].

	Together, the analyses conducted using data from the pivotal ALLEGRO-2b/3 provide evidence that generic preference-based instruments, EQ-5D and SF-36, administered in the trial are not valid measures of HRQoL in AA. Both measures demonstrated issues with construct and content validity, responsiveness, with substantial observed ceiling effects across known patient groups. These results confirm the high ceiling effects, lack of content validity, and reduced sensitivity/responsiveness observed in previously submitted findings (Doc B.3.4.1. **2. Qualitative assessment of content validity** The company submission outlines the inconsistency between: the qualitative assessment of the burden of the condition (that the company, patient groups and clinicians believe is significant); the utility values published in the literature (Doc B.3.4.3); and data from the ALLEGRO 2b/3 trial (Doc B.1.3.2.3 and B.3.4.1). This was reinforced through the patient advisory group study and Delphi therapeutic treatment panel, which showed that EQ-5D is too broad and does not capture all the impacts faced by patients with AA in a meaningful way (Doc B.3.4.4.2, Figure 6). These gaps were in the domains of social functioning, relationships, emotional, physical, appearance and financial. In the omission of these elements of HRQoL, which are important to patients with AA, the EQ-5D lacks content validity (Figure below). Further, clinician feedback (as summarised in Section B.3.4.4.2) advised that the administration of EQ-5D is not specific enough to AA and so the 'health questions [are] ambiguous for an AA sufferer'. The evidence points to EQ-5D capturing some but not the full burden of the condition (Doc B.1.3.2.3, B.3.4 and company technical engagement response pages 21-31). The company submission is consistent with the findings from the new quantitative psychometric evaluation evidence presented above.

	Figure 6: Aspects of HRQoL not covered by the HRQoL generic measures.[11]  The company has provided comprehensive evidence to demonstrate that EQ-5D captures some but not all the HRQoL burden of AA. Therefore, the original vignette time trade off (TTO) study as part of the company submission provides a viable alternative aligned with the hierarchy for preferred HRQoL methods as outlined in the methods guide (Figure 5). The company maintains that the vignettes represent the magnitude of the uncaptured value of improving SALT score as recognised by the committee and accurately reflect the significant burden on HRQoL for patients living with AA. The validity of the vignette TTO approach is further reinforced in comment 4 where the company presents (new evidence) an extension of the vignette TTO in the UK AA patient population showing comparable estimates with the original vignette TTO in the UK general population. The company also presents a multi-component scoping review providing new conceptual overlap evidence that validates the vignette TTO utility estimates by comparing utility values generated in a proxy condition which has comparable HRQoL burden from a patient perspective (comment 4).
4	**Utility values of patients with severe AA from the Vignette TTO study are representative of the HRQoL impact for patients with AA. The company has provided two additional sources of evidence in line with the preferred HRQoL methods as outlined by NICE that reinforces the face validity of the utility estimates further.**

The committee agree that the company followed best practice when doing the original vignette TTO in the general population, although committee concerns remained around the validity of the results. The company have generated a further two sources of evidence in line with the preferred methods to reinforce the face validity of the original vignette TTO results and to reduce decision uncertainty on the magnitude of uncaptured benefit. The evidence supports the company position that generating utility values through vignette TTO is the correct approach as it captures the lived burden of the condition and is valued similarly by patients and the general population. Further, the values generated are comparable to other disease areas where a similar HRQoL burden across key psychosocial domains is experienced by patients.

1. **A replication study of the original vignette study was conducted among persons with AA to support the face validity of the TTO valuations provided by the UK general public.[12]**

The study results demonstrate the burden of AA to patients and provides a novel set of patient-derived utility values for HRQoL in AA. The TTO studies, both in the general public and in an AA population demonstrate the substantial HRQoL burden for patients with AA which increases with greater hair loss. The patient and UK public (general population) utility weights are compared in Figure 7. The comparison shows a similar trend across health states between the patient and UK public samples with the wide range in scores for each health state reflecting heterogeneity in the patient sample. Considering the means and confidence intervals there is no evidence to suggest that the ratings from patients with AA are any different to the general public. The AA utilities elicited using the vignette descriptive system and TTO better capture HRQoL impacts for AA patients and potential treatment benefits in cost effectiveness analysis. An updated company base case scenario using the AA patient TTO utility values is presented in Table 2

Table 2: Cost-effectiveness results with the Company's base case and including results from the vignette TTO from patients with AA.

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]	-	-	-
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	7,767

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

2. **A multi-component scoping review was conducted to identify utility values from a "proxy" condition, which has a similar impact on health-related quality of life as AA, from the patients lived experience perspective. Atopic dermatitis was identified as the proxy condition and utility values overlap with the utility values from the vignette TTO.[13]**

Atopic dermatitis (AD) was identified as the most relevant proxy condition based on numerous overlapping patient-relevant domains including impacts on emotional and physical wellbeing, as well as relationships, social interactions and stigma (Figure 8 and Figure 9). Utility estimates overlap with utility estimates derived from the vignette TTO (mean scores as low as 0.62 for the UK) with lower values seen in patients with co-morbidities (e.g., levels of depression, sleep disturbance or sexual dysfunction (Figure 7). [14-18] It is worth noting, that in the context of AD and the EQ-5D, overlap in utility values is not seen consistently across the literature, implying that the EQ-5D also often fails to capture the full burden of dermatological conditions, particularly in clinical trial settings, a point which was acknowledged by the committee in TA681.[13, 19] Further indicating the short-comings of the EQ-5D in capturing the full burden of these conditions. The company have included an updated scenario using a central estimate of utility values by severity (mild, moderate, severe) for atopic dermatitis (assumed to be comparable to mild moderate and severe AA) from Table 5. The ICER based on company base case results is presented in Table 3.

Table 3: Cost-effectiveness results with the Company's base case and including central utility estimates for mild, moderate and severe derived from a comparable proxy condition, atopic dermatitis.

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]			-
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	17,973

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Further Detailed Evidence

1. **An extension of the original vignette TTO in which a sample of people with the condition complete the EQ-5D VAS and TTO based on the vignette to derive health state utilities. The resulting utility values from patients with AA are consistent with the values derived from the general population.**

	The key objective of this non interventional, cross-sectional study (N=50) was to estimate the utilities for health states describing AA using TTO interview with patients with AA. This work follows the original vignettes and TTO interviews in the general population (Doc B.3.4.4.3). Utility values observed in the original vignette TTO study had a wide range ([redacted]), with ratings for the most extensive hair loss states indicating a substantial perceived burden. The uncertainty raised by the committee is that the public had overestimated the impact of AA on HRQoL, and their scores did not reflect the extent to which patients adapt and cope with their condition over time. Therefore, the decision was taken to undertake further valuation work, this time with patients as the participants. This study was designed to further explore the validity of the vignettes and to also compare patient derived utilities with the general public derived utilities for each health state. **Study Design** Study design including protocol and sample characteristics can be found in the accompanying report. In summary, previously developed and validated health state vignettes describing different extensiveness of hair loss were included (Doc B.3.4.4.3) In addition, a vignette describing the HRQoL of a caregiver of an adolescent with AA was also included. All vignettes were reviewed and valued using the TTO method during the interviews. **Results** The patient and UK public (general population) utility weights are compared in Figure 7. The comparison shows a similar trend across health states between the patient and UK public samples with the wide range in scores for each health state reflecting heterogeneity in the patient sample, with some participants going to lead-time for the higher SALT score health states. Considering the means and confidence intervals there is no evidence to suggest that the ratings from patients with AA are any different to the general public.

Figure 7: Patient and UK Public Utility Weights in AA

Note: Error bars show 95% confidence intervals.

Qualitative Observations;

For the AA population sample, the vignettes were well comprehended by patients and unexpected preferences were justified. All patients reported that the vignettes content was representative of their lived experience of AA to some extent, thus indicating their face validity. The majority of patients reported that at least one specific health state accurately described themselves currently or at a previous stage of hair loss. The remainder indicated that a mixture of health states or some aspects from each description fit their experience. For example, some participants commented that they do not limit social activities but do limit physical activities, whereas one participant commented that they would not limit physical activities.

Patients drew on their own experience when valuing the vignettes, for example, one patient acknowledged the impact of AA beyond simply hair loss stating, “It’s just hair”, but knew from personal experience there were additional burdensome impacts, which adversely affects their HRQoL. Social activities and mental wellbeing were commonly reported as the most important determinants of trading time. Some participants considered the loss of eyebrow hair as significantly worse because this cannot be concealed, whereas others saw the severity between the health states with and without eyebrow hair loss as immaterial and valued them similarly or the same.

Discussion

Patient derived health state utilities were lower for health states which described a greater extent of hair loss. The findings were consistent with those observed in the previous study with the UK general public. Caregiver HRQoL impact was also demonstrated.

Through this study, patients with AA have reviewed the contents of the vignette, and confirmed they are an accurate representation of their lived experience, thus confirming their face validity. The endorsement of the vignettes in this study suggests that the content was broadly accurate. Therefore, health state utilities in both value sets are representative of the impact experienced by patients with AA.

The study results demonstrate the burden of AA to patients and provides a novel set of patient-derived utility values for HRQoL in AA. Both TTO studies in the general public and an AA population demonstrate the substantial HRQoL burden for patients with AA which increases with greater hair loss. The is consistent with impact as described by patients and acknowledged by the committee. The AA utilities elicited using the vignette descriptive system and TTO better capture HRQoL impacts for AA patients compared with generic measures such as EQ-5D and SF-36. The results of this study confirm the internal validity of the original vignette TTO through both the content of the vignettes and a validation of TTO ratings generated from the general public. An updated company base case scenario using the utility estimates from vignette TTO in the AA population results in an ICER of £7,767/QALY.

2. A conceptual overlap analysis to identify utility values from a "proxy" condition, which has a similar impact on health-related quality of life as the condition of interest. Atopic dermatitis was identified as the proxy condition and utility values overlap with the utility values from the vignette TTO.

The company have conducted a multi component scoping review study to collate and describe utility values for a proxy condition, which is conceptually similar to AA in terms of patients lived experience and HRQoL. Atopic dermatitis (AD) was identified as the most relevant proxy condition based on numerous overlapping patient-relevant domains including impacts on emotional and physical wellbeing, as well as relationships, social interactions and stigma. These domains are reported to substantially influence HRQoL for patients with AD, further mirroring similarities to the lived experience of patients with AA.[4-6] Utility value estimates for AD from the literature range from 0.40-1.00 regardless of utility measure, statistical measure, sub-population, treatment or timepoint. [14-18, 20-34] Mean scores across all severities are as low as 0.62 for the UK. [21] Furthermore, the utility values identified indicate that patients with more severe AD have a lower HRQoL than those with mild or moderate disease. The lowest scores for AD were seen where patients with AD suffered from various levels of depression, sleep difficulties or sexual dysfunction and patients with different body locations of AD.[14-18] It is worth noting, that in the context of AD and the EQ-5D, overlap in utility values is not seen consistently across the literature, implying that the EQ-5D also often fails to capture the full burden of

dermatological conditions, particularly in clinical trial settings, a point which was acknowledged by the committee in TA681.[13, 19] Further indicating the short-comings of the EQ-5D in capturing the full burden of these conditions.

A full report is provided separately. In summary patients with AD feel the majority of their HRQoL burden in similar domains to patients with AA aligned to the conceptual work in AA already conducted by the company (Figure 6).[6] Within AD a wide range of utility values have been generated across a range of settings and measures. We have collated these utility values, to the best of our ability. Limiting factors include reporting on disease severity and differences in setting. Based on additional evidence presented, the utility values estimated in the vignette study falls within the range of values generated for AD where the lived experience of patients is very similar. The results confirm the representativeness of the original vignette TTO in capturing the HRQoL burden in AA.

Further Detailed Information

Demonstrating potential HRQoL benefits of novel therapies is a key factor in drug approval. However, as mentioned previously, there is currently a paucity of HRQoL utility data, including EQ-5D, for patients with AA in the UK. The objective of this multi-component scoping review was to collate and describe the range of utility values that exist in the literature for a conceptually similar condition. A structured electronic search (2013–2023) was conducted to identify conceptual models for similar chronic conditions which have overlapping HRQoL domains with AA, considered important from a patient perspective. A further structured electronic search for utility data for the proxy health condition was conducted to identify studies conducted in Australia, USA, Canada, New Zealand, Europe, the Nordics or globally. Additionally, published NICE HTAs were identified to understand the methodological approaches used for modelling utility values in the proxy condition. Utility values and utility methodology were extracted and summarised.

AD was identified as the most relevant proxy health condition for AA based on numerous overlapping HRQoL domains.[4, 35-37] Both conditions impact patients physically, emotionally and psychologically whilst also causing stigma, and affect relationships, social activities and lifestyle. AA and AD are also similar in their pathogenesis and aetiology,[38] are common comorbid conditions of one another,[39, 40] and parallels have been drawn between the two diseases in several studies.[4, 38, 41, 42] Given this, AD is a valuable candidate to be used as a proxy health condition to demonstrate the HRQoL of AA patients. Utility estimates for AD from the literature range from 0.40-1.00 regardless of statistical measure, sub-population,

treatment or timepoint. [14-18, 20-34] Mean scores across all severities are as low as 0.62 for the UK.[21] Notably, the utility values reported in RCTs tended to be higher than the values reported in RWE studies, although this discrepancy may be due to treatment effect and/or exclusion criteria for those with impacted mental health. Furthermore, the utility values identified indicate that patients with more severe AD have a lower HRQoL than those with mild or moderate disease. The lowest scores for AD were seen where patients with AD suffered from various levels of depression, sleep difficulties or sexual dysfunction and patients with different body locations of AD. [14] [15] [16] [17] [18] These are correlated with conceptual models for AA as outlined in Figure 8 and Figure 9.

Figure 8: Conceptual model for adult and adolescent AD taken from Grant et al. 2019[5]

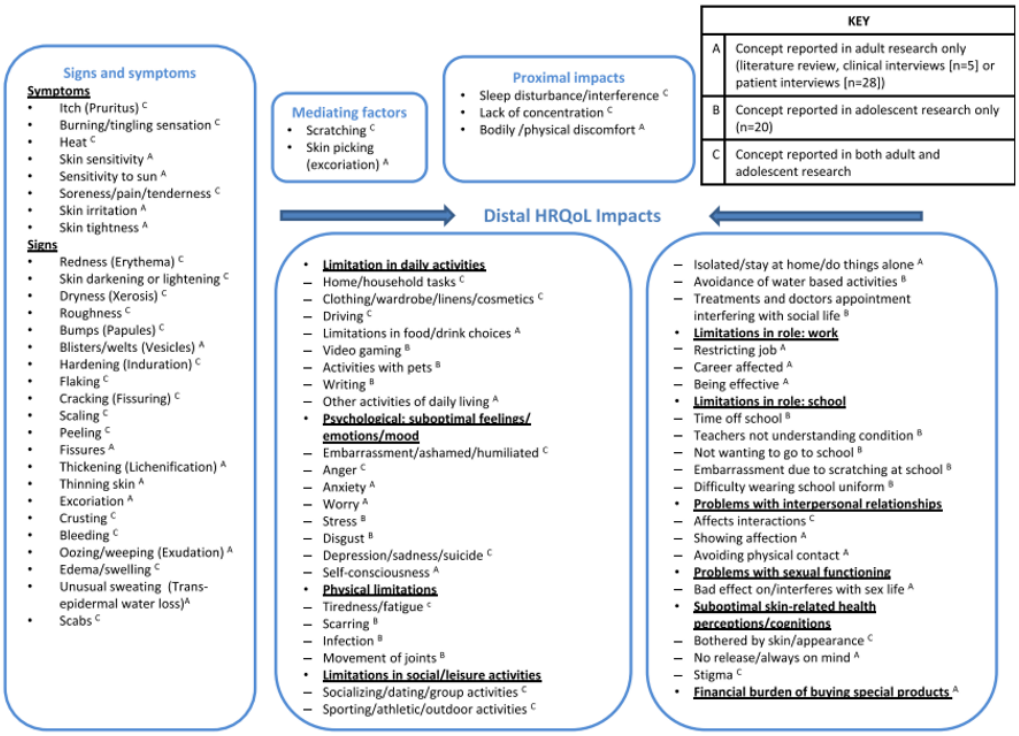
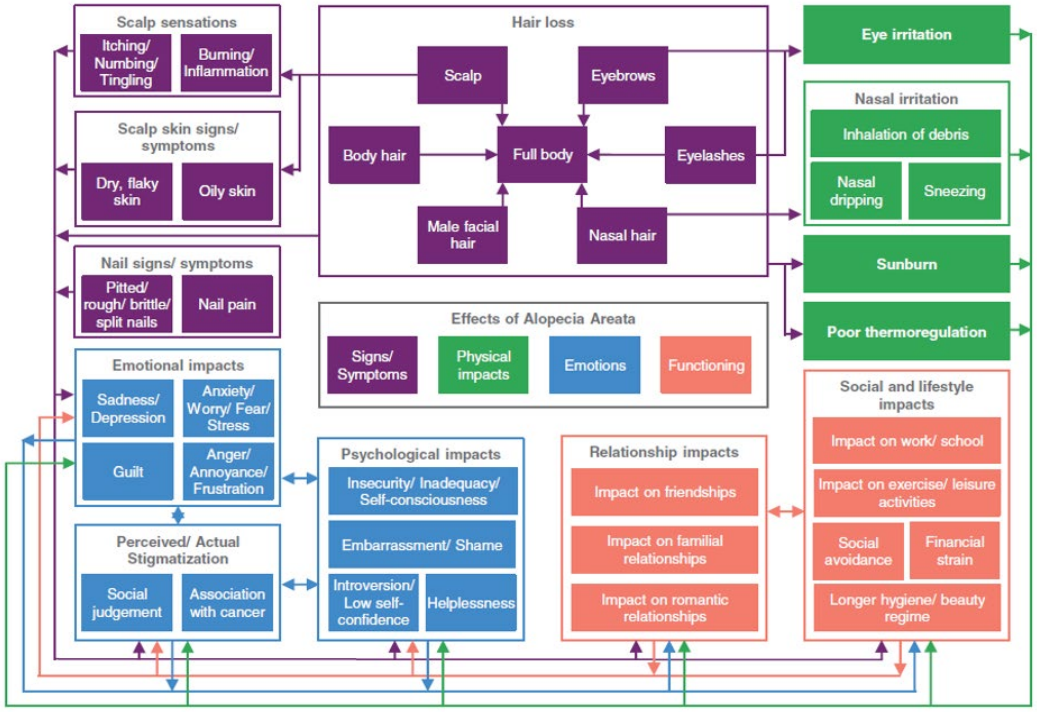


Figure 9: Conceptual model for AA taken from Aldhouse et al. 2020[4]



Three NICE technology appraisal (TA) submissions for moderate to severe AD from the past five years were identified: TA534 for dupilumab, TA681 for baricitinib, and TA814 for upadacitinib, tralokinumab and abrocitinib.[19, 43, 44] All submissions used EQ-5D utility scores sourced from their relevant phase 2b/3 RCTs and these were cross-walked to the standard EQ-5D-3L scores using the van Hout et al. 2012 algorithm where necessary, and valued using the UK value set.[45, 46] Utility values were reported for responders and non-responders and modelled as a function of response to treatment at week 16 in all submissions.

Mean utility values reported ranged between 0.51–0.90 across all treatments and timepoints, fitting within the range identified in other studies included in this review for moderate to severe AD patients. Overall, the key comments from the EAG were that response-based utility values are more appropriate than treatment-specific utility values only. Hence, all submissions incorporated utility values for both responders and non-responders for each treatment. For TA681, the model used in the company submission was deemed as too simplistic by the EAG as it did not distinguish between different levels of response, therefore, utility values were amended to those from TA534 which had already been accepted by the committee.[19 44] Further details can be found in table 12, 13 and appendix D of the report.

Assuming AA and AD disease severities to be comparable in terms of patient lived experience and HRQoL (given the similarities highlighted above), the utility values for AA from the TTO analysis sit within the ranges of utilities identified for AD across all studies in this review (Table 5). The lower bounds of the AD ranges suggest that AD patients have a lower HRQoL than AA patients. Conversely, the upper bounds suggest that moderate and severe AD patients have a better HRQoL than moderate and severe AA patients. These trends also apply to studies including a UK population specifically, except for mild disease, where the AA utility is slightly higher than the upper bound of AD utilities identified. Some of this variation may be due to heterogeneity in study designs, geographical locations and populations used in each study, as well as the subjective nature of HRQoL in patients.

Table 4: AA utility values identified in a UK vignette study by Pfizer compared to AD utility values identified in this review

Disease severity	AA				AD	
	Health States (n = 120)	TTO utility weights*			Mean range in utilities	
		Mean	SD	95% CI	All studies	Studies including a UK population
Mild	SALT 0-10	[redacted]	[redacted]	[redacted]	**0.73–0.92†**	**0.78–0.88†**
	SALT 11-20	[redacted]	[redacted]	[redacted]		
Moderate	SALT 21-49	[redacted]	[redacted]	[redacted]	**0.64–0.91‡**	**0.68–0.91‡**
Severe	SALT 50-100	[redacted]	[redacted]	[redacted]	**0.42–0.91‡**	**0.42–0.91‡**
	SALT 50-100 + eyebrow/eyelash loss	[redacted]	[redacted]	[redacted]		

*TTO data identified in a UK vignette study by Pfizer (data on file); †Mean; ‡Mean or unspecified measure

Abbreviations: AA, alopecia areata; AD, atopic dermatitis; CI, confidence interval; SALT, Severity of Alopecia Tool; SD, standard deviation; TTO, time trade-off

It is important to note that AA utility values reported in other studies report inconsistent findings. The study (Bewley et al.) suggested by the committee within the ACD as a preferred source of utility (0.78–0.90), also broadly fit within the ranges of utilities identified for AD in this review albeit at the lower end with a narrow range.[47-49] However, an exception to this is the utility values generated in two studies using the EQ-5D-5L for mild, moderate and severe AA patients

	from the US and Europe (Appendix F, full report), which reported higher utility values than the TTO values below (Table 14 full report).[48, 49] This disparity in EQ-5D-5L values across studies further highlights the issue that the EQ-5D often fails to capture HRQoL improvements in people with skin conditions, a point which was acknowledged by the committee in TA681 submitted to NICE.[19] An updated company base case scenario using the central estimates from the utility values identified for mild, moderate and severe AD results in an ICER of £17,973/QALY
5	**Further evidence to demonstrate that generic and condition-specific preference-based measures of health-related quality of life are not suitable for estimating utility values for use in the model.** New evidence • Section 2 provides additional longitudinal evidence evaluating EQ-5D in the ALLEGRO-LT over 24-36 months showing high ceiling effects and no changes in EQ-5D scores over time (mean and by SALT state). • Section 3 includes additional psychometric evaluation of EQ-5D and SF-36 from the ALLEGRO 2b/3 study provides evidence that EQ-5D and SF-36 are unresponsive to changes in HRQoL. • Section 4 presents additional new evidence from a related proxy condition, AD. The results show utility values estimated in the vignette study falls within the range of values generated for AD where the lived experience of patients is very similar. The results confirm the representativeness of the original vignette TTO in capturing the HRQoL burden in AA. The new evidence is presented in addition to that already provided in the company submission based on: • trial results interpretation (Company submission Doc B.3.4.1) • our systematic literature review to identify and summarise the best available HRQoL evidence available for the treatment of AA, and targeted literature review searches to

identify utility values in the literature as part of our vignette study development (Company submission Doc B.3.4.3.)

- our qualitative assessment through the PAG study and Delphi Panel (company submission Doc B.3.4.4.2.). This evidence is consistent with what we have heard from patients and clinicians at appraisal committee meetings for both Baricitinib (TA681) and Ritlecitinib (ID4007).

All evidence presented throughout the company submission demonstrates both quantitively and qualitatively that generic measures of health-related quality of life are not suitable for estimating utility values for use in the model. Additionally, from our searches, no condition-specific preference-based measures exist for AA. Therefore, no generic or condition specific measures are appropriate for use in the cost effectiveness model.

To summarise, our literature search found that the reported degree of difference in HRQoL evaluated using generic HRQoL measures between mild moderate and severe are small and values are often close to population norms, which is not aligned to the patient-described burden (Doc B.3.4.3 and Appendix A).[50-53] This suggests that the extent to which generic measures of HRQoL capture the full burden of AA may not align with the impact as described by patients with the condition.[4, 6] Despite the lack of alignment, the committee's preferred assumption is to use the utility values from Bewley et al.[49] However, based on the submission of evidence and testimony from clinicians and patients together with additional published conceptual analysis on the HRQoL burden of AA, the narrow range identified by Bewley et al. between mild moderate and severe health states is not fully captured by EQ-5D.[4, 5] Therefore, this represents an overly conservative estimate of HRQoL impact for patients with AA. Previous appraisals have acknowledged the potential limitations of EQ-5D in AA and dermatological conditions. We welcome the committee's acknowledgement of uncaptured value in the current ACD (section 3.20, ACD).

Alternatively, the generic SF-36 and AQoL-8D measures have been used in previous studies with AA patients. However, neither instrument has been validated for use within the AA population. Further, literature on the SF-36 implies significant heterogeneity in five of the eight SF-36 dimensions within the AA population.[54, 55] Several studies have also indicated that the SF-36 may not fully represent the burden of health-related quality of life in patients with AA.[54, 55] which aligns with our qualitative assessment (company submission Doc B.3.4.4.2.). The AQoL-8D has been used in two studies of AA, conducted in Australia, the data of which was statistically insignificant.[47, 56] Further, there is currently no available UK population norms for the AQoL-8D measure.[56]

	Additionally, from our searches, no condition-specific preference-based measures exist for AA. AAPPO is not a preference-based measure, so utilities cannot be derived, even indirectly. The DLQI measure is commonly used in clinical practice to assess the HRQoL in AA patients (Doc B.3.4.3). However, the DLQI refers to skin problems, rather than hair, raising concerns about its content validity and relevance to AA patients, as evidenced through our qualitative assessment (company submission Doc B.3.4.4.2.). Whilst we acknowledge that clinicians use the DLQI in practice for patients with AA they often have to modify or substitute words in the questionnaire to make it more relevant to an AA patient.[57] While the DLQI has been mapped to the EQ-5D to produce utility values, taking this approach for AA would rely on using mapping algorithms developed for other conditions, e.g., psoriasis (as recognised by the EAG, Page 132-133 of the EAG report). The limitations of the DLQI measure for AA patients, coupled with the limitations surrounding the lack of appropriate disease-specific mapping algorithm, and the suitability of the EQ-5D in terms of content validity (as suggested by the EAG, Page 130 of the EAG report), implies that mapping the DLQI to the EQ-5D for AA patients would be inappropriate, as suggested by Longworth & Rowen, 2013.[58] Therefore, no generic or condition specific measures are appropriate for use in the cost effectiveness model.
6	**Other utility sources preferred by the committee based on Bewley et al, remain unable to characterise the entire HRQoL burden of living with AA. Any under estimation based on this source of utility potentially underestimates the value of new treatments and represents uncaptured value.** The Committee state that the utilities in Bewley et al. were based on longer-term evidence than the EQ-5D reported in ALLEGRO 2b/3 so may be more sensitive to changes in health-related quality of life. Whilst the company agree that the Bewley et al. utilities are more representative of the HRQoL of patients with AA than the utilities reported in the ALLEGRO 2b/3 study, they disagree that they are more sensitive due to being based on longer-term evidence.[49] Conversely, the Bewley et al. utilities are not based on long-term evidence. In the survey, enrolled patients completed a single questionnaire informing HRQoL whilst disease severity was informed by clinician opinion. There is no longer term evidence informing HRQoL over time according to disease severity. The company hypothesises that the Bewley et al. utilities demonstrated more sensitivity to severity of AA given that patients with major psychiatric conditions do not appear to be excluded from participating in the survey.

	However, despite the inclusion of patients with major psychiatric conditions, the company maintain that the Bewley et al. utilities remain unable to characterise the entire HRQoL burden of living with AA for the following reasons: • Only an abstract and poster is available, which limits the ability to truly scrutinise the robustness of the methodology undertaken. • The severity of AA is informed by subjective physician judgement of mild, moderate or severe AA as opposed to objective SALT scores. The definition of disease severity also limits the suitability of using the utility values in the economic valuation, due to the misalignment with the model structure. • The EQ-5D instrument is used, which the company maintains is unable to characterise the full HRQoL burden of living with AA. This is demonstrated in the wide overlap of the confidence intervals for the point estimates of EQ-5D in the Bewley et al. study. Since the committee meeting, a full manuscript has become available for the Bewley et al. study, published by Vañó-Galván et al.[3] Despite the availability of the manuscript in full, limitations remain for the subjective judgement of severity of AA and use of the EQ-5D instrument. The committee also refer to a Japanese study of a similar design to characterise HRQoL in patients with AA.[59] Whilst a full manuscript is available for this study, it remains unsuitable for use for the following reasons: • Severity of patients' AA is informed by subjective physician judgement of mild, moderate and severe AA which does not align with objective SALT scores. • HRQoL is measured in Japanese patients, which may not reflect the burden of AA to patients in the UK. • The EQ-5D instrument is used, which may not capture the full burden of the condition. Given the company's position on generic measures of HRQoL. Further evidence on the validity and responsiveness of different utility measures are provided in response to comment 3 in this document. In conclusion, the utilities in the literature remain inappropriate to characterise the full burden of AA to patients. As such, use of utilities from the literature will underestimate the full

	benefits of treatment with ritlecitinib in patients with AA and so the cost-effectiveness of ritlecitinib compared to BSC would remain underestimated.
7	**The company base case does not include pharmacological treatments within its definition of best supportive care. This is conservative given the conclusions of the committee in the most recent appraisal of Baricitinib for AA.[1]** The Committee has concluded that given the inconsistent use of pharmacological treatments for severe alopecia areata and the uncertainty around whether people would use pharmacological treatment after stopping ritlecitinib, it was acceptable to include only non-pharmacological treatment options in the best supportive care health states. However, pharmacological treatment costs in BSC were accepted in the baricitinib NICE appraisal (TA926).[1] Therefore, it should be taken into consideration that the assumption to only include non-pharmacological treatments of BSC is conservative. It is anticipated that the costs associated with the basket of pharmacological treatment of BSC would be greater for patients treated with BSC only compared to patients who discontinue ritlecitinib. This is because patients who have engaged with ritlecitinib are less likely to engage with off-licence low-efficacy BSC treatments compared to patients who have not received any licensed treatments, as discussed in TA926.[1] During consultation for the NICE appraisal of ritlecitinib, clinical experts also suggested that differential usage of pharmacological treatments as part of BSC would be seen for patients following discontinuation of ritlecitinib, stating that pharmacological treatments would be offered on a case-by-case basis, depending on treatment history and patient preference. To highlight the possible impact of including pharmacological costs of BSC on the cost-effectiveness of ritlecitinib, the Company has explored different scenarios in the economic model in which BSC pharmacological treatments have been included. To implement scenarios including the pharmacological costs of BSC, the resource use for pharmacological treatments within BSC were sourced from the baricitinib NICE appraisal (TA926).[1] The cost per pack for each treatment were sourced from the BNF. The cost, dosing regimen, frequency and duration of each treatment are presented in Table 5. **Table 5: Drug acquisition cost for BSC**

Treatment	Dose and frequency	Pack size	Cost per pack (£)	Proportion of patients in BSC (%)

				Adelphi DSP	UK KOL input
Ciclosporin	4mg/kg daily	100mg/tablet, 30 tablets	41.59	13.72	12.50
Methotrexate	20mg weekly	2.5mg/tablet, 24 tablets	1.33	12.86	7.50
Azathioprine	2mg/kg daily for one year	50mg/tablet, 100 tablets	3.07	2.57	8.67
Intralesional steroids (triamcinolone acetonide)	5mg biweekly	40mg/vial, 5 vials	7.45	9.43	30.83
DPCP (contact immunotherapy)	Weekly treatment for 9 months	1 bottle	124.00	21.63	27.50
Prednisolone	0.4mg/kg daily	5mg/tablet, 28 tablets	0.48	17.15	25.00
Topical corticosteroids (Mometasone scalp lotion)	2ml daily	30ml/bottle, one bottle	4.36	24.77	63.33
Minoxidil 5% foam (topical)	1g Males twice daily up to 24 weeks if no improvement. Females once daily up to 16 weeks if no improvement.	180g, one bottle	45.63	5.72	37.50
Minoxidil tablets	20mg daily	10mg/tablet, 60 tablets	30.68	0.00	7.50
Mycophenolate mofetil	1,000mg twice for one year.	500mg/tablet, 50 tablets	6.36	2.86	0.00
Anthralin 0.1% cream	1.5g daily for 23 weeks.	50g/bottle, one bottle	3.77	5.72	0.00
Patients receiving no active treatment				12.00	13.00
Source	NICE TA926.[12]	British National Formulary. The cost of contact immunotherapy was sourced form Fisher Scientific.[13] The cost of anthralin 0.1% cream was not identified on the British National Formulary so was sourced from NICE TA926.[12]		NICE TA926.[12]	

Abbreviations: BSC, best supportive care; DPCP, Topical immunotherapy with diphencyprone; DSP, Disease Specific Programme; KOL, key opinion leader; NICE, National Institute for Health and Care Excellence; TA, technology appraisal, UK, United Kingdom

When estimating the costs associated with pharmacological treatments of BSC, conservative assumptions were made. First, it was assumed that no further treatment monitoring costs were incurred beyond those already captured in the model. Second, it was assumed that

there was no wastage. These assumptions were made to ensure avoidance of double counting of monitoring costs of patients with severe AA.

As highlighted by the Committee, as well as the Committee of the baricitinib NICE appraisal (TA926),[1] there is considerable uncertainty associated with the composition of pharmacological treatments used as BSC and whether patients who have discontinued ritlecitinib would continue to receive pharmacological treatments as part of BSC. To explore this uncertainty, the Company has explored the same scenarios considered by the Committee in TA926.[1] This includes:

- Using both Adelphi DSP and UK KOL derivations of the resource use associated with pharmacological treatment in BSC (presented in Table 6),
- Adjusting to the proportion of patients who discontinue ritlecitinib that go on to receive pharmacological treatments as BSC compared to patients in the BSC arm:
    - no adjustment,
    - reductions of 25%, 50% and 75% of patients receiving pharmacological treatments of BSC on discontinuation of ritlecitinib relative to patients who receive BSC only.

To align with the Committee's preferred assumption in TA926, it was assumed that pharmacological treatments of BSC would be administered over a ten-year time horizon. The resulting cost of BSC per cycle is presented in Table 6.

Table 6: Acquisition cost of BSC per cycle

Reduction to pharmacological BSC costs applied to patients receiving ritlecitinib	Ritlecitinib (£)	BSC (£)
Adelphi DSP		
0%	261.12	261.12
25%	195.84	261.12
50%	130.56	261.12
75%	65.28	261.12
UK KOL inputs		
0%	328.27	328.27
25%	246.21	328.27
50%	164.14	328.27
75%	82.07	328.27

Abbreviations: BSC, best supportive care; DSP, Disease Specific Programme; KOL, key opinion leader; UK, United Kingdom

The impact of including the pharmacological treatments of BSC on the cost-effectiveness estimates of ritlecitinib compared to BSC using the Company's base case is presented in Table 7. In each case, the ICER when including the pharmacological treatment costs of BSC is less than the ICER when not including pharmacological treatment costs of BSC, showing that not including pharmacological treatment costs of BSC is conservative. When including pharmacological treatment costs of BSC, the ICER ranges between £74 and £6,743. Given the lack of evidence regarding the use of BSC following ritlecitinib and the inconsistent use of pharmacological treatments as part of BSC, the full range of ICERs presented across these scenarios should be considered in decision-making.

Table 7: Cost-effectiveness results with the Company's base case and including pharmacological treatment as BSC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Base case (BSC, no pharmacological treatment)					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	8,294
Adelphi DSP – 0%					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	6,743
Adelphi DSP – 25%					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	5,105
Adelphi DSP – 50%					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	3,467
Adelphi DSP – 75%					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	1,830
UK KOLs – 0%					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	6,322
UK KOLs – 25%					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	4,239

UK KOLs – 50%						
BSC	[redacted]	[redacted]				
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	2,156	
UK KOLs – 75%						
BSC	[redacted]	[redacted]				
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	74	

Abbreviations: BSC, best supportive care; DSP, Disease Specific Programme; ICER, incremental cost-effectiveness ratio; KOL, key opinion leader; QALY, quality-adjusted life year; UK, United Kingdom

8

Increasing the proportion of adolescents in line with clinical practice as outlined in the ACD reduces the overall ICER compared with the company base case. Therefore, the current company base case estimate is conservative.

In the ACD, it is reported that the clinical experts advised that '*the proportion of young people included in the ALLEGRO trials underrepresented the proportion seen in clinical practice*'.

In the ALLEGRO 2b/3 trial, 14.6% of patients were adolescent and 85.4% were adults. However, in response to an evidence request from the committee following the ACM, the company provided the ICER weighted by the prevalence of adults and adolescents with AA within the general population. The diagnosed point prevalence of AA is 0.58% and [redacted]% amongst adults and adolescents, respectively.[60] Applying these prevalence data to the adolescent and adult population in England suggests that 95% and 5% of patients with AA are adults and adolescents, respectively (Table 8). This does not align with the statement reported by the clinical experts (i.e., >14.6% AA population in their UK clinical practice is adolescent).

Table 8: Proportion of patients with AA who are adolescents and adults of those aged 12+

	Adolescents	Adults	Source
Total population in England	3,918,423	44,456,850	Office for National Statistics (ONS) CCG mid-year population estimates
Diagnosed prevalence of AA (%)	[redacted]	0.58	RCGP data
Population in England with AA	13,323	257,850	Total population × diagnosed prevalence
Proportion of patients with AA of people aged 12+ (%)	4.91	95.09	-

Abbreviations: AA, alopecia areata; CCG, Clinical Commissioning Group; ONS, Office for National Statistics; RCGP, Oxford-Royal College of General Practitioners

Therefore, the ICER weighted by age submitted by the company in response to the evidence request assumed that there were fewer adolescents than adults. As displayed in Table 9 and Table 10, ritlecitinib is more cost-effective within the adolescent population than in the adult population. If the ICER was weighted in line with the clinical experts' opinion, the ICER would be closer to the ICER of the adolescent population. Moreover, by increasing the proportion of adolescent patients with AA, in line with clinical expert opinion, the ICER would be lower than the company's base case following technical engagement. As such, the anticipated ICER of ritlecitinib compared to BSC is likely lower than the company base case and is therefore conservative to ritlecitinib.

Table 9: Cost-effectiveness results with adolescence only population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	7,986

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life year

Table 10: Cost-effectiveness results with adult only population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	8,940

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life year

9 **The long term extrapolation of time on treatment based on treatment waning effect and extrapolation of long term data is conservative to ritlecitinib**

The committee have concluded that people taking ritlecitinib would likely stop treatment rather than taking it indefinitely. Our previous discussions with clinicians about their experience reinforces that AA is a chronic condition and patients will remain on treatment for the long term (Company technical engagement response 4 (p13) and 6 (p17)). [7] Data from the ALLEGRO-LT study supports stabilisation of the proportion of patients achieving a response as summarised in Figure 10 and Figure 11 for SALT≤20 responders (This is consistent with SALT≤10 responders, company technical engagement response 6 (p17)). No treatment waning effect together with the uncensored analysis of discontinuations provided

in the company technical engagement response supports a higher time on treatment than that preferred by the committee.

Figure 10: ALLEGRO-LT: Response Based on SALT ≤ 20 up to Month 24 (Interim Analysis Selected cohorts, 200/50 mg dose)

Abbreviations: CI, confidence interval; QD, once daily; SALT, Severity of Alopecia Tool.
Note: n/N indicated for each timepoint: N = number of patients with observed data, n = number of patients achieving SALT ≤10. The ALLEGRO-LT trial is ongoing; therefore, a lower number of patients appear at later timepoints.
Source: Pfizer data on file. Long-Term PF-06651600 for the Treatment of Alopecia Areata (ALLEGRO-LT) - Interim Analysis. 2023.[61]

Figure 11: ALLEGRO-LT: Response Based on SALT ≤ 20 up to Month 24 (Interim Analysis Selected cohorts, 50 mg dose).

Abbreviations: CI, confidence interval; QD, once daily; SALT, Severity of Alopecia Tool.
Note: n/N indicated for each timepoint: N = number of patients with observed data, n = number of patients achieving SALT ≤10. The ALLEGRO-LT trial is ongoing; therefore, a lower number of patients appear at later timepoints.
Source: Pfizer data on file. Long-Term PF-06651600 for the Treatment of Alopecia Areata (ALLEGRO-LT) - Interim Analysis. 2023.[61]

Further discussions with clinicians acknowledge that there may be instances where patients, through specific circumstances, may wish to try a treatment holiday or taper their treatment. But, as the committee acknowledge, there is no evidence for this. The company argue based on clinician feedback that this remains in the minority for those patients who continue to respond. Given there is no evidence to the contrary the company argue that a more appropriate estimation of time on treatment includes the assumption of stay in state as there is no evidence of treatment waning in patients who are responding and is the most appropriate assumption based on clinical opinion.

Figure 12 below outlines the various scenarios from the model and the cost effectiveness esimates are in Table 11. The company asks that if the preferred assumptions of the committee remain then we request it is acknowledged as a conservative assumption whilst remaining cost effective when applied to the company base case.

Figure 12: Time on treatment based on assumption of treatment waning and long term discontinuation combined.

Table 11: Cost-effectiveness results with changes to time on treatment assumptions

Scenario	Total BSC costs (£)	Total BSC QALYs	Incremental costs of ritlecitinib (£)	Incremental QALYs of ritlecitinib	ICER of ritlecitinib compared to BSC (£)
Committee Scenarios					
Committee unweighted base case (using Bewley abstract)	[redacted]	[redacted]	[redacted]	[redacted]	28,633

	Committee unweighted, time on treatment ([redacted] yrs): Stay in state, Weibull	[redacted]	[redacted]	[redacted]	[redacted]	23,914
	Committee unweighted, time on treatment ([redacted] yrs): Stay in state, exponential	[redacted]	[redacted]	[redacted]	[redacted]	24,022
	Committee weighted, time on treatment ([redacted] yrs): Stay in state, gen gamma	[redacted]	[redacted]	[redacted]	[redacted]	24,615
	Committee weighted, time on treatment ([redacted] yrs): Stay in state, gompertz	[redacted]	[redacted]	[redacted]	[redacted]	25,172

10

Factual inaccuracies

1. In Section 3.6 of the ACD, it is stated that *"The population in ALLEGRO 2b/3 included young people aged 12 to 17 years (14.5%) and adults (85.4%)."*

   However, this is incorrect. The majority of participants were adults, 613 to be exact (85.4%); a total of 105 (14.6%) adolescents were enrolled.[14] Therefore, the Company asks that the above text be changed to the following:

   "The population in ALLEGRO 2b/3 included young people aged 12 to 17 years (14.6%) and adults (85.4%)."

2. In Section 3.15 of the ACD, regarding caregiver disutilities, it is stated that *"The Committee accepted that it is plausible that the impact of severe alopecia areata is not limited to the person with the condition but may also have an effect on family members of adolescents. It concluded that the Company's approach was acceptable and made little difference to the cost effectiveness estimates. So, it concluded that it was appropriate to include disutilities for carers of young people in the model."*

The Company has accepted the Committee's suggestion and only applied caregiver disutility to caregivers of adolescents. However, the Company would like the £1,050 increase to the ICER resulting from the exclusion of caregiver disutilities for adults with AA to be considered (Table 12 and Table 13, respectively). Feedback obtained from patient advisory groups (PAGs) and dermatologists with a specialist interest in hair disorders, support the evidence that caregiver disutility is relevant to both the caregivers of adults and adolescents with AA.[11, 41, 62]

Table 12: Cost-effectiveness results without caregiver disutility applied to adults (adolescents only)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	8,294

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life year

Table 13: Cost-effectiveness results with caregiver disutility applied to adults (adolescents and adults)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	7,685

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life year

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Appendix A

Targeted Literature Search Utility estimates in Alopecia Areata. Objective 3: Methodology

Summary of objective

Generating utilities using the EQ-5D directly with patients is the preferred option recommended by the National Institute for Health and Care Excellence (NICE) for cost effectiveness analysis. Where this is not possible, the next best alternatives are to obtain EQ-5D utility values from the literature or use a mapping algorithm to generate EQ-5D data (1). Where EQ-5D is shown to be inappropriate, based on qualitative empirical evidence on the lack of content validity and evidence that it performs poorly on tests of construct validation (i.e., does not perform as would be expected), NICE recommends using other generic preference-based measures, such as the SF-36, condition-specific measures, such as the DLQI, or vignette studies for obtaining utilities.

It was hypothesised that standard preference-based measures of HRQoL may not be sensitive to capture the full impact of hair loss associated with AA and so this review also aimed to explore the use of EQ-5D, SF-36 and the Dermatology Life Quality Index (DLQI) for utility generation and how sensitive these instruments are for detecting differences in HRQoL by extensiveness of hair loss and treatment response. The DLQI has been used in dermatology to estimate utility weights via a mapping algorithm (2). Findings from this review will highlight what utility data have been published in patients with AA and will summarise the appropriateness of these instruments for generating utility data.

Search strategy

Based on the most recent NICE health technology evaluations manual (1) this review was focused on primary research studies which reported utility values from generic preference-based measures (EQ-5D and SF-36) or utility data that had been estimated using mapping from DLQI.

In addition, the search was designed to identify any studies that had included the DLQI more broadly and assessed its sensitivity in detecting differences in HRQoL by the extent of hair loss in patients with AA. This was included to determine if DLQI derived utilities could differentiate between different severities of hair loss (2). Articles reporting psychometric validation of these measures in an AA population were also noted if identified in the search.

The search was conducted via OVID using MEDLINE, Embase and Psychinfo databases. The search terms are available in Table 1. The same inclusion and exclusion criteria used for the burden search (objective 1) were applied for this search with the requirement that HRQoL be measured using one of the three

instruments of interest (Table 2).

Table 1: Search terms

Search Terms
Alopecia [title/abstract] OR Alopecia Areata [title/abstract] OR Total alopecia areata [title/abstract] OR Alopecia totalis [title/abstract] OR Alopecia universalis [title/abstract] OR Patchy Alopecia Areata [title/abstract] OR Ophiasic Alopecia Areata OR Ophiasis [title/abstract] OR Universal Alopecia Areata [title/abstract] AND EQ-5D [title/abstract] OR EQ-5D-3L [title/abstract] OR EQ-5D-5L [title/abstract] OR EuroQol [title/abstract] OR Dermatology life quality index [title/abstract] OR DLQI [title/abstract] OR SF-12 [title/abstract] OR short-form 12 [title/abstract] OR SF-36 [title/abstract] OR short-form 36 [title/abstract] OR SF-6D [title/abstract] OR short-form 6D [title/abstract]

Table 2: PICOS for use of EQ-5D, SF-36 and DLQI in AA search

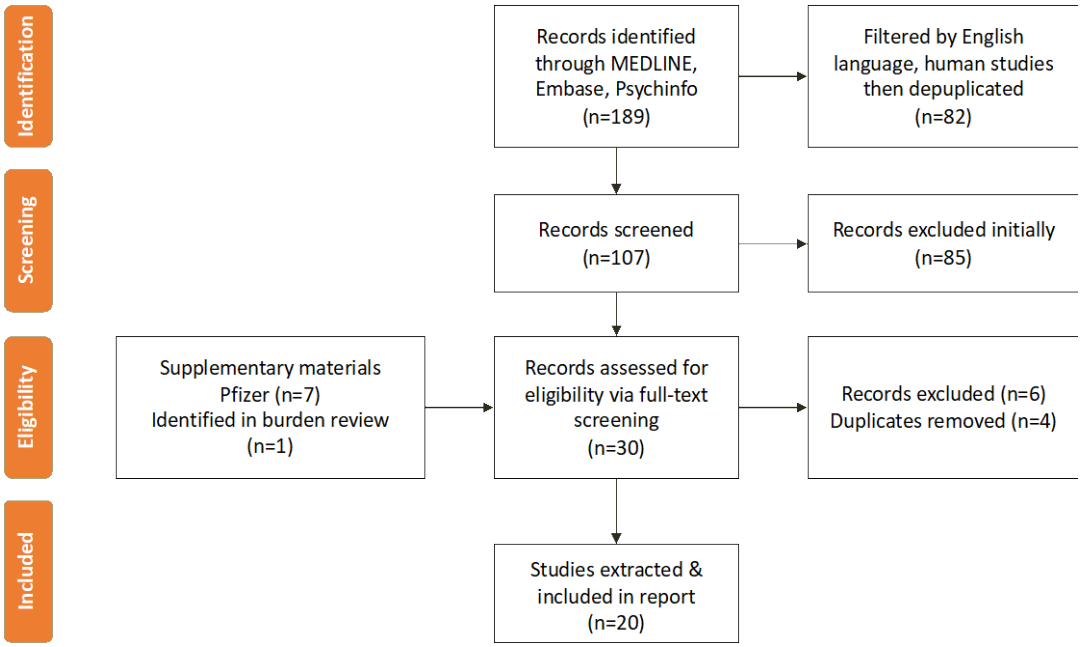
i. Population	• Human subjects • Males and Females aged 12+ (inclusive) • Patients with any AA subtype (e.g., AU, ophiasis) • Other hair loss conditions and non-AA conditions were excluded
ii. Interventions/comparators	• Interventional and non-interventional studies included • No limit by treatment or dependent on comparator or no comparator
iii. Outcomes	• HRQL measured by EQ-5D, SF-36 or DLQI (utilities mapped to EQ-5D)
iv. Study Designs	• Quantitative cross-sectional or longitudinal studies • Clinical trials with relevant HRQL endpoints
v. Other	• Manuscripts/abstracts must be available in English

Objective 3: Results

Results

A flow diagram detailing the review process is shown in Figure 1. The initial search returned 189 papers, reduced to 107 by filtering for available in English language, human studies and deduplication. A total of 85 articles were then excluded after title/abstract review. These papers were screened to 30 papers to be assessed for full-text eligibility. This included 8 additional papers that were identified as relevant from alternative sources; one was identified in the objective one search that also met the current inclusion criteria, the other seven were identified through Pfizer's materials on file. A total of 20 papers were subsequently identified for data extraction. Key characteristics of included studies are outlined in Appendix Table 1. The summary of these findings will be used to evaluate the appropriateness of the EQ-5D, SF-36 and DLQI and their sensitivity to capturing differences in HRQoL by the extent of hair loss in patients with AA.

Figure 1: Flow chart detailing extraction process



Summary of study characteristics

Among the 20 included studies utilising the EQ-5D, SF-36 and DLQI the most frequent instrument was the DLQI (n=15) followed by the SF-36 (n=5) and then the EQ-5D (n=2). All studies using the DLQI only reported score data and had not used a mapping function to convert this data into utility values. The

mapping function requires individual level data, so it was not possible to retrospectively generate utilities using aggregate data. Two studies also used the Assessment of Quality of Life- 8D (AQoL-8D) (3,4). Despite this not meeting our original inclusion criteria, it was included because it also provided utility values and there is a mapping function available for estimating EQ-5D utility values using domain scores (5). A total of 13 studies explored differences in HRQoL by the extent of hair loss (4,6–17) Of these, only 2 reported utility values according to the extent of hair loss (i.e., the AQoL-8D study, and a study reporting EQ-5D-5L analyses) (4,12). No identified studies reported the validation of the SF-36 or EQ-5D in an AA population suggesting that they may have limited validity in this population and may not be sensitive to HRQoL impacts associated with AA.

Utility values in patients with AA

Four studies were identified that reported utility values in patients with AA (3,4,12,13). One observational study across 13 European countries reported presented aggregate EQ-5D results for patients with AA (n=37) compared to a control group (n=1359) (13). Boxplots were presented which indicated that median utility values were approximately 0.890, which was significantly lower than controls ($p<0.05$).

A real-world study from the US sponsored by Eli Lilly designed to understand how the severity of AA affects patients' HRQoL was identified (12). The sample consisted of adult patients who were diagnosed with moderate or severe AA or with a history of moderate/severe AA. The study reported EQ-5D-5L utility values by physician-rated AA severity categories of mild (n=56), moderate (mild=140) and severe (n=65). Severity was rated subjectively by the physician based on the patient's medical history and an assessment during the consultation. Values of 0.95, 0.93 and 0.87 were observed for mild, moderate and severe, respectively (12). While the differences between severity groups were statistically significant ($p<0.05$), the degree of difference between each group was quite small and very close to US population norms (5). The findings suggest that that the EQ-5D may not capture the full impact of AA.

One study reported a randomised trial conducted in Australia designed to explore the impact of cyclosporin treatment in patients with moderate to severe AA. Thirty-two patients were randomised to receive cyclosporin or placebo and were assessed for three months. HRQoL was assessed using the AQoL-8D, a multi-attribute utility instrument developed in Australia (4). HRQoL was reported in terms of the extent of hair loss (4). Baseline utility scores for both groups overall were 0.748, slightly lower than the population norms for Australia (0.80). The authors report that patchy alopecia had a higher health utility (mean= 0.773; standard deviation, SD=0.127) than AU and AT (0.732, SD=0.256). Improvements in AQoL-8D utility values were observed over the 3-month follow up in both the cyclosporin (0.064) and placebo groups (0.050). No statistically significant differences were seen in utility values by age (ages 18-30 = 0.678 vs. ages 46-65 = 0.789) or gender (Male = 0.791, Female = 0.738). Another study investigating the treatment of AA with

tofacitinib in a group of 16 patients with patchy AA, AU and AT observed a mean SALT score reduction of 15.57 (%) from baseline over 12 weeks which was associated with an AQoL-8D utility improvement (0.515) over this period (3).

In addition to the four studies reporting utility data, an additional study using the SF-36 among 60 patients with AA found that all SF-36 domains apart from physical functioning and bodily pain were more impaired in patients with AA compared to controls, with vitality and mental health domains being most severely impacted (19). It would be possible to generate a utility value at the sample level; however, differences by extensiveness of hair loss were not explored.

Other HRQoL outcomes by extensiveness of hair loss

A total of three studies using the SF-36 assessed relationships between HRQoL and extensiveness of hair loss. One cross-sectional study (16) reporting on 50 patients with AA from Tunisia compared differences in SF-36 domain scores by different SALT score categories. Individuals with 51-75% of scalp hair loss had lower social functioning domain scores (SF = 21.66 ± 32.5) compared to those with less than 25% scalp hair loss (SF = 64.83 ± 29.19), suggesting greater social functioning impairment in individuals with more extensive hair loss. Mental health domain scores were also lower for individuals with complete hair loss (MH =44 ± 21.66) compared to those with 51-75% hair loss (MH = 56.66 ± 20.61) (16). Utility values have previously been estimated with these data at Pfizer using a mapping algorithm for an early economic model.

In contrast, another study conducted in Iran explored the impacts of AA on SF-36 scores (n=100) and showed no significant differences by extensiveness of hair loss (categories: <25%, 26-50%, 51-75%, 76-100%) (7). SF-36 domain scores are not reported in this study so it would not be possible to use a mapping function to estimate utilities. One study reports SF-36 domain scores for the whole sample but not by extensiveness of hair loss, so it would only be possible to generate utility values using a mapping function for the whole sample and not by degree of hair loss (15).

Ten out of the 15 studies using the DLQI explored HRQoL differences by extensiveness of hair loss but five did not (8,20–23). All studies reported DLQI data directly and did not convert these scores to utility data. Of these ten studies, seven cross-sectional studies from different countries showed that greater hair loss was significantly associated with poorer HRQoL based on DLQI scores (6,7,9,11,13–15). Of note:

- Jankovic et al., reported on a cross-sectional study of patients with AA (n=60) recruited from a hospital in Belgrade. Significant differences were observed for all DLQI domains by extensiveness of scalp hair loss (SALT categories: mild [0-25%], moderate [26-75%], severe [76-100%]) and proportion of total body hair loss (categories: 100%, some body hair loss, no body hair loss) (15).

- Abedini et al., also report significantly lower DLQI scores for mild (<25% hair loss) AA compared to severe (AU/AT, Ophiasis) AA (5.4±6.8 vs. 10.7± 7.5) in a sample of 176 patients with AA from Iran. The analysis from this study also showed that the association was independent of other confounding factors, such as disease duration, gender and occupation (11).

- A study of 655 patients with AA in China also observed significantly higher DLQI scores in patients with AU/AT (DLQI = 8) compared to patchy AA (DLQI = 5.1), although extent of hair loss captured within the patchy AA category was not reported (9).

- A 7-year cohort study of 2962 patients with AA in an outpatient clinic in Kuwait observed significant differences in DLQI scores between extensive (>50% scalp hair loss) AA (DLQI = 13.37), AT (DLQI = 13.5) and AU (DLQI = 14.1) (6).

- In a study of 40 patients with AA and scalp hair loss of ≥20%, mean DLQI scores improved from 9.95 at baseline to 5.31 at week 24 after undergoing treatment. This was associated with a mean SALT score improvement of 27.1% (8).

Two studies using both the DLQI and SF-36 observed an association between extent of hair loss and HRQoL according to the DLQI but not the SF-36, possibly indicating that the DLQI is more sensitive to differences in disease severity (7,15).

Two studies showed no significant association between DLQI scores and extensiveness of hair loss (10,17). However, among these studies, one reported borderline significant differences (p=0.071) between mild and severe AA in patients with AA and androgenetic alopecia (n=178) (17), while the other study may have been underpowered to detect significant differences due to the small number of patients included with ³25% hair loss (10).

Conclusion

The results of this review show that there is limited literature regarding the use of preference based HRQoL measures in AA, with very few studies reporting utilities by extensiveness of hair loss. Only two studies reported EQ-5D utility data in patients with AA. One study presents EQ-5D scores for the whole sample but utilities were not reported by extensiveness of hair loss (13). Another study reported EQ-5D data according to AA severity, but severity was measured subjectively by physicians and not using SALT scores, as per Pfizer's economic model (12). One study reported utility values using the AQoL-8D for patients by extensiveness of hair loss, but extent of hair loss was defined as patchy, AU and AT (4). It is possible to

map the AQoL-8D to EQ-5D utility estimates using the AQoL-8D domain scores, but domain scores are only reported graphically in this study. Notably, none of the studies using the SF-36 reported utility values. A few studies reported SF-36 domain scores (7,15,16,22), which could be mapped to estimate EQ-5D utilities; however, only one study reported SF-36 domain scores by extensiveness of hair loss (29).

Overall, there is limited evidence regarding the sensitivity of the EQ-5D in assessing the impact of AA on HRQoL. One study reported statistically significant differences in EQ-5D utilities between patients with different degrees of hair loss, but the absolute differences in scores were small (12). This is inconsistent with the broader literature that suggests an important HRQoL impact in patients with AA that increases with more extensive hair loss (24–27). This could suggest that the EQ-5D is not sensitive to the full impact that AA has on HRQoL.

Evidence on the sensitivity of the SF-36 to the impact of AA on HRQoL was mixed. One study showed that the extensiveness of scalp hair loss was related to poorer mental health and social functioning domain scores, but two other studies showed no relationship with domain scores. Overall, the limited evidence suggests that the SF-36 may not be sensitive to the range of HRQoL impacts associated with AA.

The majority of studies using the DLQI showed that more extensive scalp and total hair loss was related to poorer DLQI scores across all HRQoL sub-domains. This suggests that the DLQI may be more sensitive to the HRQoL impacts of AA compared to other preference-based measures, such as the EQ-5D and the SF-36. Although a utility mapping function is available for the DLQI, it is difficult to determine the impacts on utility values without patient-level DLQI data. Overall, evidence from this review suggests that the EQ-5D and SF-36 are not sufficiently sensitive to the full impact AA has on HRQoL or for detecting differences in HRQoL by extensiveness of hair loss. The DLQI appears to be more sensitive but none of the studies converted scores to utility values. No studies were found that reported validation of these measures in patients with AA and therefore the validity of these measures in this population.

NICE National Institute for Health and Care Excellence

Ritlecitinib for treating severe alopecia areata in people 12 years and over [ID4007]

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Appendix Table 1: Key information of studies identified in objective 3 search					
First author	**Title**	**Year**	**Sample**	**HRQoL/utility instrument**	**Key findings**
Burge	The patient-reported burden of alopecia areata by current severity: a real-world study in the United States	2020	261 adults	EQ-5D-5L, Skindex-16, WPAI	• More severe AA was associated with lower EQ-5D utility values. • Emotional domain as measured by the Skindex-16 and activities outside of work as measured by the WPAI were the most impacted HRQoL domains.
Titeca	'The psychosocial burden of alopecia areata and and androgenetic alopecia': a cross-sectional multicentre study among dermatological out-patients in 13 European countries	2020	115 patients with hair diseases, 37 with alopecia areata, 1359 controls	DLQI, HADS, EQ-5D, EQ-VAS	• Age, sex and comorbidity matched patients with AA had poorer HRQoL (EQ-5D, DLQI, EQ-VAS) than AGA patients and controls • AA severity impacted HADS scores but not DLQI
Yu	Illness perception in patients with androgenetic alopecia and alopecia areata in China	2016	212 androgenetic alopecia and 130 alopecia areata patients	DLQI	• Extensiveness of hair loss not related to DLQI scores in AA or AGA • Significant scores for concerns and emotional illness perceptions caused psychological distress and low HRQoL
Jankovic	Quality of life in patients with alopecia areata: a hospital- based cross-sectional study	2016	60 adults	SF-36, Skindex-29, DLQI	• More severe categories of AA (Mild, Moderate, severe) associated with greater HRQoL impairment in DLQI dimensions of symptoms/feelings and daily activities • Work/school was the only DLQI

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					dimension not more significantly impacted in AU/AT patients • SALT scores directly correlated with daily activity and treatment DLQI sub-domains and social functioning Skindex-29 domain
Ferhatoğlu	Type D personality and quality of life in alopecia areata and vitiligo patients: A cross-sectional study in a Turkish population	2020	39 adults	HAD-A, HAD-D, DLQI	• No significant difference in prevalence of type D personality in AA compared to control groups • No differences by extensiveness of hair loss observed
Ghajarzadeh	Depression and quality of life in Iranian patients with Alopecia Areata	2011	100 adults	SF-36, DLQI,	• Greater HRQoL impairment (DLQI) associated with more extensive hair loss • No relationship between HRQoL impairment (SF-36) and extensiveness of hair loss
Abideen	Quality of life in patients with alopecia areata attending dermatology department in a tertiary care centre - A cross-sectional study	2018	60 adults	DLQI, GHQ-28	• 70% of sample had impaired HRQoL • AU, AT and Ophiasis had greater HRQoL impairment (DLQI) compared to patchy AA
Abedini	Quality of life in mild and severe alopecia areata patients	2018	176 adults	DLQI	• Patients with mild AA had less impaired HRQoL than patients with severe AA • Patients with acute stress within 6 months of study had poorer HRQoL
Zhang	Quality of life assessment in patients with alopecia	2017	178 adults	DLQI	• Extensiveness of hair loss did not impact HRQoL (DLQI)

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	areata and androgenetic alopecia in the People's republic of china				• Greater HRQoL impairment observed in younger patients, those with AA >12 months
Shi	Health-Related Quality of Life (HRQoL) in Alopecia Areata Patients—A Secondary Analysis of the National Alopecia Areata Registry Data	2013	N/A	Skindex-16, DLQI	• No HRQoL difference by severity reported • Greater HRQoL impairment in patients between the ages of 20-50, females and patients with changes in physical appearance (hair loss, nails, skin)
Masmoudi	Quality of life in alopecia areata: A sample of Tunisian patients	2013	50 adults	SF-36	• More extensive hair loss was associated with poorer SF-36 mental health and social functioning domains
Al-Mutairi	Clinical profile and impact on quality of life: Seven years experience with patients of alopecia areata	2010	2962 adults	DLQI	• More extensive hair loss was associated with greater HRQoL impairment (DLQI) with AT and AU patients showing the greatest impairment respectively
Vélez-Muñiz	Psychological Profile and Quality of Life of Patients with Alopecia Areata Skin Appendage Disorders	2019	94 adults, 32 children	DLQI, HADS	• 77% of adults with AA assessed with the DLQI showed HRQoL impairment • 65.9% of adults showed signs of depression or anxiety according to the HADS • No differences observed between HRQoL and extensiveness of hair loss
Lai	Impact of cyclosporin treatment on health-related quality of life of	2019	32 adults	AQoL-8D	• Patchy Alopecia had a higher health utility (0.773) compared to AT/AU (0.732) this difference was not significant

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	patients with alopecia areata				
Lambert	A novel multidisciplinary educational programme for patients with chronic skin diseases: Ghent pilot project and first results	2011	55 skin disease patients, 2 with alopecia areata	DLQI	• Mean DLQI score of 6 presented for 2 patients • Extensiveness of hair loss data not captured
Dubois	Quality of Life in Alopecia Areata: A Study of 60 Cases	2020	60 adults	SF-36	• No HRQoL differences by the extensiveness of hair loss were observed • Patients had poorer HRQoL SF-36 domain scores for mental health and vitality compared to controls
Meier	Treatment of therapy resistant alopecia areata with fumaric acid esters	2015	40 adults	DLQI	• Individuals with SALT scores <20 at baseline had impaired HRQoL as measured by the DLQI
Nasimi	Alopecia Areata-quality of life index questionnaire (reliability and validity of the Persian version) in comparison to Dermatology life quality index	2020	100 adults and adolescents (16<)	DLQI	• Mean DLQI of 10.69 presented • HRQoL differences by extensiveness of hair loss were not assessed
Qi	Profile of alopecia areata in 655 Chinese patients	2010	655 adults	DLQI	• HRQoL impairment (DLQI) was higher in AU/AT patients compared to patchy • Patients with recurrent disease had greater HRQoL impairment (DLQI)

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Lai	Sublingual tofacitinib for alopecia areata: a roll-over pilot clinical trial and analysis of pharmacokinetics	2021	20 adults	AQoL-8D	• AQoL-8D Utility value for patients with moderate to severe AA improved by 0.05 from baseline to 12 weeks

Appendix A References

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Ritlecitinib for treating severe alopecia areata in people 12 years and over [ID4007]

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Appendix B

Utility estimates from the ALLEGRO 2b/3 and ALLEGRO-LT studies

The health state utility values based on the longest available EQ-5D data from the ALLEGRO 2b/3 (Table 13) and ALLEGRO-LT (Table 14) are provided. The data shows no difference in utility estimates overtime between the ALLEGRO 2b/3 (up to 48 weeks) and ALLEGRO-LT (24 months). The data reinforces that there is no change in utility estimates regardless of time on treatment. The company reiterates that these results are inconsistent with the acknowledged impact on quality of life for patients with severe alopecia areata.

Table 14: Mixed model regression utility estimates ALLEGRO 2b/3 48 weeks (Adults only)

Covariate	Utility Weight	Standard error
SALT 50-100	[redacted]	[redacted]
SALT 21-49	[redacted]	[redacted]
SALT 11-20	[redacted]	[redacted]
SALT 0-10	[redacted]	[redacted]

LSM and SE from a mixed-effects model for repeated measures with fixed effects categorical salt group (4 categories), centered baseline utility (continuous), centered age (continuous), and random effects subject ID.
EQ-5D-5L mapping algorithm code (STATA/R packages) EEPRU paper[7]

Table 15: Mixed model regression utility estimates ALLEGRO-LT 24 months (Adults only)

Covariate	Utility Weight	Standard error
SALT 50-100	[redacted]	[redacted]
SALT 21-49	[redacted]	[redacted]
SALT 11-20	[redacted]	[redacted]
SALT 0-10	[redacted]	[redacted]

LSM and SE from a mixed-effects model for repeated measures with fixed effects categorical salt group (4 categories), centered baseline utility (continuous), centered age (continuous), and random effects subject ID.
EQ-5D-5L mapping algorithm code (STATA/R packages) EEPRU paper[7]
Modified de novo (MDN) results from B7981032 include de novo participants who met inclusion criteria 5 of Study B7981015.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Alopecia UK

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Alopecia UK Unrestricted research grant of £50,026.28 received from Pfizer in 2022. For research around the psychological impact & economic burden of alopecia areata. Now ceased Eli Lilly - £20,000 received in 2023 as corporate sponsorship. Pfizer – Alopecia UK is a member of the Pfizer sponsored Patient Organisation Leaders Forum. Travel expenses paid to Lynn Wilks as member attending meetings and small consultancy fee to be paid to Alopecia UK for two, two hour meetings attended
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No links to or funding from the tobacco industry
Name of commentator person completing form:	Lynn Wilks

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**<u>Has all of the relevant evidence been taking into account.</u>** We understand that NICE has to make a decision based on the clinical trial and other data submitted by Pfizer in respect to ritlecitinib. We ask the committee to really consider the feedback from the patient and clinical experts, which we think explained, the devastating effect on mental health and considerable psychosocial impacts for people

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	with severe alopecia areata. (As per 3.1) "The committee concluded that severe alopecia areata has wide ranging effects and can have a profound impact on quality of life'. Maybe the committee can consider the over 10,000 people who signed a petition to the government on the NICE rejection of baricitib (reply released 14th December) We note your reference to the 'average person' but please consider those most affected by alopecia areata: • One study has reported rates of mental health challenges as high as 47.5% in people with alopecia, 35.5% anxiety and 29% depression (Montgomery K et al, A Mixed methods survey of social anxiety, depression and wig use in alopecia. BMJ open, 2017 Apr 1;7(4):e015468) • For newly diagnosed patients with AA studies suggest that people are more likely to develop depression and anxiety disorders (Macbeth AE tell al. The associated burden of mental health conditions in alopecia areata: a population based study in UK primary care. British Journal of Dermatology. 2022 Jul 1;187(1):73-81 We are disappointed that, as is usual for clinical trials in people with severe alopecia areata, those persons with severe mental health challenges e.g. anxiety and depression and suicide ideation will have been excluded from this trial. We believe that this group of people would be those that would show lowest quality of life at baseline and greatest improvement in quality of life from taking ritlecitinib and having hair regrowth. It is a real shame that data from these people is not part of your assessment, and this is noted by the committee in section 3.12 ' The committee noted that the utility values represented the quality of life for the average person'. We want to highlight that as people with severe depression and suicidal ideation would be excluded from this that the impact on this group of people could be higher, as could the improvement in quality of life from hair regrowth, and this group should be considered for access to ritlecitinib from the NHS
2	**<u>Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?</u>** We believe that people with severe alopecia areata, continue to suffer with a lack of any licenced pharmaceutical treatment available from the NHS possibly because there is not an appropriate pharmacological comparator which could be used in a NICE assessment, and hence demonstrate better cost effectiveness. It is sad for us to think that maybe just by adding in a higher wig allowance or more people being referred to a dermatologist i.e. stronger best supportive care, that the set £30K cost per qualy could be hit. The reality is that people with severe alopecia areata continue to be abandoned by the NHS. As the committee states ' there is an unmet need for a new treatment' (Section 3.2), so we are ever hopeful that Pfizer can provide the data to NICE to reach that elusive cost effectiveness number, and that the NICE committee look beyond the uncertainties in modelling, which just reflect the sad uncertainty for people with severe alopecia areata. Eli Lilly for baricitinib, and Pfizer for ritlecitinib, used EQ5D in their clinical trials, as that is what is stated as the standard measure in the NICE manual and there is no other, routinely used, quality of life measure for alopecia areata. In this assessment and draft guidance it is good to see that (section 3.13) the committee and EAG seem to agree on the limits of EQ5D – so we hope that Pfizer can satisfy your requirements for further data.

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	We must re-state how we feel that EQ-5D is an inappropriate measure for quality of life in alopecia areata, as only one of the domains (anxiety/depression) is relevant to psychosocial impacts in severe alopecia areata. See above for the references related to the degrees of anxiety and depression and suicide ideation suffered by people with severe alopecia areata. As a patient organisation of lay persons, section 3.14 just confused and frustrated us. The committee does not seem willing and flexible enough to accept the vignettes that were put forward by Pfizer. Yet reading the excerpts of your manual, a vignette is listed as an acceptable tool (section 3.13 and section 4.3 of NICE's health technology evaluation: the manual (2022). Also, in section 3.12, the EAG stated that 'the company had followed best practice to develop the vignettes'. The patient and clinical experts 'suggested that for some people with suicidal thoughts their utility value could be as low as that estimated for the most severely affected'. I am the patient expert who raised the effects on my quality of life of severe alopecia areata compared to my brain haemorrhage recovery. We ask NICE to accept the data from the vignettes that Pfizer have submitted rather than searching for the quality of life impacts on the 'average person'. Alas, the over 40% people with mental health challenges will have been excluded from ritlecitinib trials and hence their data will not be available to you. For people who have considerable anxiety, depression and psychosocial impacts, we believe that these vignettes could be a reality. Yet, you do accept Bewley, a poster presentation from the EAG. And hence we see the see-saw again- Pfizer demonstrate that ritlecitinib is cost effective but then with a different measure from the EAG it is not cost effective. The Bewley poster clearly showed that even with EQ5D, and JUST considering the anxiety and depression domain that those with severe alopecia areata 'reported lower QoL and higher anxiety/depression than those with mild/moderate AA' We want to stress again, the percentage of patients with severe alopecia areata with severe anxiety and depression who would have been excluded from the trials, hence the weakness of the broad trial data. We understand that the Bewley poster data has now been published (Vano-Galvan et al. Physician and Patient Reported Severity and Quality of Life Impact of Alopecia Areata… Dermatol Ther (2023) 13:3121-3135) and it does show the negative effects on quality of life from severe alopecia areata. We want to raise a couple of key points from that paper • 'Physician understanding of the full patient burden of AA beyond hair loss is important to ensure the appropriate treatment and support is given' – as we have mentioned many times, it is psychosocial impact that is just as important as % hair loss. We ask the committee to listen to the clinical experts and stakeholders to how much this treatment is needed for routine commissioning from the NHS • 'Minimal impact was seen on the other EQ-5D-5L dimensions, which seems consistent with the age of respondents and the limited physical impact of AA beyond hair loss' – we believe this is further acknowledgment of the weakness of the EQ-5D tool for assessing QoL in severe alopecia areata and hence why just using EQ5D from trial data is inappropriate, as we mentioned throughout this process and feedback

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	While we acknowledge the need for cost effectiveness for the NHS, we just ask the committee to consider people with severe alopecia areata, for which there are currently No effective, licensed treatments available from the NHS.
3	**Are the recommendations sound and a suitable basis for guidance to the NHS** NO – Alopecia UK does not think that the recommendations are sound and a suitable basis for guidance to the NHS. We do not think it is 'suitable' to deny people with severe alopecia areata access to one of the first licensed products to treat their disease. Pfizer have submitted data and calculations to demonstrate cost effectiveness of ritlecitinib, so why does the committee not accept those? A NICE rejection of ritlecitinib means that people with severe alopecia areata continue to be neglected (abandoned) by the NHS, where there is currently no standard patient pathway (and there never has been), long delays and limitations for referral to secondary care specialists (with some NHS dermatology departments declining appointments for alopecia patients), no licensed pharmaceutical treatments available from the NHS (although two licensed treatments now exist) and limited acknowledgement and support for the psychosocial impacts of this disease. We want to highlight the points that the committee has acknowledged and noted, in support of the approval of ritlecitinib for routine commissioning in the NHS: Section 3.1 'The committee concluded that severe alopecia areata has a wide-ranging effects and can have a profound impact on quality of life'. At Alopecia UK, we hear of the young adults who have quit education or work because of severe mental health challenges and those who suffer from suicide ideation and even those who have committed suicide over having alopecia. We also hear and understand the improvements of quality of life with hair regrowth, people describing to us about 'getting their life back' but because of a weak and inappropriate QOL measure and no standard pharmaceutical comparator, this licensed treatment is denied. Section 3.2 'The committee concluded that there is no standard care for severe alopecia areata, that treatments are not equitable across England & Wales, and that there is an unmet need for new treatments'. Only 3 or 4 patients in 10 will be referred from the GP to a dermatologist and we hear of some NHS Trusts who are now not accepting referrals for alopecia areata because of high workloads, and a prioritisation of other diseases. Even if you are referred the wait to see a dermatologist is likely to be over 12 months. The few, off-licence treatments are rarely prescribed, ineffective and it really is a post code lottery even to receive 'best standard of care'. Section 3.3 'The committee concluded that ritlecitinib is an innovative medicine and JAK inhibitors provide a new mechanism of action for treating severe alopecia areata' The JAK inhibitors are the first licensed treatments for severe alopecia areata, they are more effective than other non-licensed treatments (like cyclosporine & methotrexate) and do show improvements in quality of life (even though those suffering the most are excluded from the trials). What we at Alopecia UK do not understand is how can the JAK inhibitors

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	be deemed cost-effective for similar, chronic, non-life threatening treatments such as psoriasis and atopic dermatitis, yet not for severe alopecia areata Section 3.23 'The committee did not have a cost-effectiveness estimate that reflected all its preferred assumptions. But the analysis which most closely reflected these resulted in an ICER above the range that is normally considered a cost-effective use of NHS resources'. We would like to challenge the committee that instead of a focus on 'preferred assumptions', that they could really listen and take into account the input from the clinical and patient experts around the unmet medical need for ritlecitinib and accept the cost effectiveness calculations from Pfizer based on the vignette data, to let this first in class of pharmaceutical treatments be available from the NHS to those most in need. We believe we are at risk of entering a future of 'haves and have nots', in which the only people who can access treatment for severe alopecia areata are those who can afford to purchase medication privately (which we know is already happening) whilst those who rely on treatment via the NHS miss out on these innovative, clinically effective treatments. This would be completely unfair and inequitable and a disgraceful situation for those already struggling with alopecia areata to find themselves in.
4	**Avoidance of unlawful discrimination…** The committee commented that 'given that the cost-effectiveness estimates preferred by the committee were not within the range usually considered a cost effective use of NHS resources……the committee were unable to make recommendations for these groups' We find this comment very disappointing. This again shows that people with alopecia areata are abandoned by the NHS. While we understand that subgroup data may not have been available from the clinical trials and not presented by Pfizer, Alopecia UK would like to highlight that severe alopecia areata is three times more likely in those with Asian/African ethnicity, hence putting them at further disadvantage. We already raised the fact that loss of head and beard hair can lead to further discrimination in some religious and cultural groups. Severe alopecia areata is associated with 'severe physical disfigurement' which is classed as a disability by the UK Disability and Equality Act 2010, therefore we view the rejection as a form of discrimination to individuals with alopecia to be denied an effective treatment that is available.
5	
6	

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- Do not include medical information about yourself or another person from which you or the person could be identified.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	British Association of Dermatologists (BAD)

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None.
Name of commentator person completing form:	**Drs Ser-Ling Chua and Leila Asfour on behalf of the British Association or Dermatologists, Prof Andrew Messenger, Drs Susan Holmes, Matthew Harries, Anita Takwale and Nekma Meah on behalf of the BAD guideline development group for alopecia areata and British Hair and Nail Society.**

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	One of the main issues in the NICE guidance for ritlecitinib is that 'best supportive care' (BSC) includes non-pharmacological treatment options – this will always be cheaper than treatment with a JAK inhibitor in economic models. Active interventions for severe alopecia areata (AA; e.g. with systemic corticosteroids +/-

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	immunosuppressive agents) would be fairer comparators (that reflect real-world practice) in health economic models. A number of systemic therapy agents are available to treat severe AA, e.g. systemic corticosteroids, cyclosporine, methotrexate, azathioprine, mycophenolate mofetil. These have been used for AA for a very long time and efficacy in AA is highly variable. Whilst available to all dermatologists, it is dermatologists with interest in treating AA who are frequent prescribers of these immunosuppressive agents for AA. Systemic corticosteroids may also be prescribed by the general dermatologists, in the context of rapidly progressive AA. Furthermore, it is also important to note, that patients with AA on small molecule/biological therapies for other indications may also benefit. This is particularly true for patients with AA and atopic eczema, receiving treatment with baricitinib or dupilumab, they may also achieve hair regrowth. These patients would not fall under the BSC scenario. Academic in confidence information removed.
2	Another issue with the guidance stems from the unwavering belief that EQ5D is an appropriate measure of QoL impairment in AA. This is despite testimony to the contrary from patients and clinical experts. We are surprised with NICE's decision given that the committee has "accepted the limitations of the EQ-5D results from the ALLEGRO 2b/3 trial.." but has still reached its conclusion not to recommend ritlecitinib based on the EQ5D data ("Ritlecitinib may improve quality of life, but it is not clear by how much"). We find a significant discrepancy in the NICE committee's approach on which utility values are being considered between the different appraisals. The NICE committee assessing baricitinib for atopic dermatitis clearly stated in their report "The committee also understood that the EQ-5D often fails to capture quality-of-life improvements for people with skin conditions. The committee concluded that, given the flaws with the company's utility values, the utility values from TA534 were preferable [meaning Eczema area and severity Index and DLQI]" (TA681; **3.16** page 27). There is unequivocal evidence in the literature of the psychosocial impact of AA, which cannot be fully captured and appreciated using the EQ-5D. A consistent approach in the choice of utility values being used in dermatology therapeutic appraisals is required to ensure there is a just process across different dermatological conditions.
3	The statements in **3.9** and **3.19** of the draft guidance do not correspond with the current evidence which suggests that patients responding well to JAK inhibitors largely appear to continue to do so. Similar to other chronic inflammatory processes such as atopic dermatitis and psoriasis, patients with severe disease often flare when stopping their systemic agent. This is similar to patients with severe AA in terms of patients with alopecia totalis or universalis. However, often their hair can regrow again when restarting a JAK inhibitor and can be maintained at a lower dose. There are limited data in terms of JAK inhibitors and safety in pregnancy. The risks in pregnancy have mainly been from animal studies; therefore, current recommendation is for women to stop medication before conception. However, there are pregnancy registries looking at safety outcomes. It is from these types of registries that we have been able to change our recommendations on other targeted therapies in recent years such as TNF-

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	inhibitors and other biologics. Therefore, our approach to JAK inhibitors in women of child-bearing potential could change over time. They can conceive after 1 month of stopping ritlecitinib which is less time compared to other immunosuppressants used in AA. While young women will have to stop treatment if they want to start a family, most patients will likely want to continue JAK inhibitor treatment if it was working well.
4	The statements in **3.12** highlight that "the vignettes only described the negative nature of the health state and did not include information on the aspects of life that were unaffected, for example mobility". Surely, the aim of the vignettes was to demonstrate the negative effect of the condition on patients. Following their comment on mobility, we are concerned that the NICE appraisal process is focusing predominantly on physical aspects, with insufficient emphasis on psychosocial impact of a condition. A UK-based epidemiological study has reported higher prevalence of depression and anxiety in people diagnosed with AA than in controls ($P < 0{\cdot}001$) and likely to be issued time off work certificates (MacBeth *et al.* BJD 2022). Another UK epidemiological study has shown AA incidence is higher in patients from areas of social deprivation and non-white ethnicity groups, whose hair can have a cultural significance (Harries *et al.* BJD 2022). Therefore, we are unsure how the comment on mobility and reflecting on other aspects can help us progress these patients care and management in these appraisals. Would the committee have suggested that patients with poor mobility reflect on aspects of their life that were unaffected, such as their hair?
5	It would also be incorrect to assume that psychological support is consistent across England and Wales. Not all hospitals are supported by clinical psychology and if even if they are, the waiting times make it difficult for timely access.
6	In section **3.15** the committee raise the question on an estimate of the proportion of young people with severe AA in clinical practice. UK-based epidemiological data has shown that AA incidence peaked at age 25–29 years in both males [IR 0·51, 95% confidence interval (CI) 0·46–0·56] and females (IR 0·43, 95% CI 0·39–0·48). The median age at diagnosis was 31 [interquartile range (IQR) 21–41] for males and 34 (IQR 22–48) for females. The incidence peak was much broader in females than males with female incidence being higher in childhood (age groups 5–14 years) and in those people aged 45+ years (Harries *et al.* BJD 2022). They do not comment on severity of disease on the primary care records. However, a higher incidence of AA in pre-adolescent and adolescent females in the current era of social media with increasing image awareness, can have a detrimental effect on their mental health. The impact of social media and image awareness on young people is echoed in the Nuffield Bioethics report [Response-from-the-Nuffield-Council-on-Bioethics-on-impact-of-social-media-and-screen-use.pdf (nuffieldbioethics.org)].

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	British Association of Dermatologists

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Ritlecitinib for treating severe alopecia areata in people 12 years and over [ID4007]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 15 December 2023. Please submit via NICE Docs.

Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	None
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Nekma Meah

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	I am concerned that best supportive care does not include pharmacological treatment and therefore does not reflect the current practice for treating alopecia areata in the UK. A number of systemic therapy agents are available to treat severe alopecia areata (AA) e.g. systemic corticosteroids, cyclosporine, methotrexate, azathioprine, mycophenolate mofetil. These have

Please return to: **NICE DOCS**

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Ritlecitinib for treating severe alopecia areata in people 12 years and over [ID4007]

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	been present for a very long time and efficacy in AA is highly variable. Whilst these treatments are available to all dermatologists, it is dermatologists with interest in treating alopecia areata who are frequent prescribers of immunosuppressive treatment in alopecia areata. Systemic corticosteroids may also be prescribed by the general dermatologists, in the context of rapidly progressive alopecia areata. Furthermore, it is also important to note, that patients with AA on small molecule therapies/biological therapies for other indications may also benefit. This is particularly true for patients with AA and atopic eczema whereby treatment for severe eczema with baricitinib or dupilumab, may also achieve hair regrowth. These patients would not fall under best supportive care options. It would also be incorrect to assume that psychological support is consistent across England and Wales. Not all hospitals are supported by clinical psychology and if even if they are, the waiting times makes it difficult for timely access.
2	I am concerned about the use of the EQ5D in alopecia areata and the utility estimates included in the model. I would like to highlight again that the EQ5D lacks face validity for AA. Importantly, only one domain is relevant to alopecia areata patients, the domain capturing anxiety and depression. The guidance recognises the significant psychological burden of AA. In my experience, the utility estimates from the vignette study are more closely aligned to that observed in clinical practice for the average patient with severe disease.
3	
4	
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Ritlecitinib for treating severe alopecia areata in people 12 years and over [ID4007]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 15 December 2023. Please submit via NICE Docs.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Single Technology Appraisal

Ritlecitinib for treating severe alopecia areata in people 12 years and over [ID4007]

Comments on the draft guidance received through the NICE website

Name	
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the DG:	

Has all of the relevant evidence been taken into account?

No. The impact on mental health of patients with alopecia areata, and especially alopecia universalis, have not been taken into consideration. Alopecia areata affects several aspects of life, it causes identity crisis, work related issues, social anxiety, identity crisis, relationship difficulties etc. It is extremely challenging in situations like exercising, dating or meeting new people. Alopecia is more than just a cosmetic issue, it has daily psychological implications, causes higher rate or sickness and unemployment, increasing chances of depression and anxiety, as well as causing infections and makes it more difficult to regulate body temperature.

Are the recommendations sound and a suitable basis for guidance to the

Based on the overwhelming evidence provided by the pharmaceutical company and Alopecia UK refusing Ritlecitinib as a treatment for Alopecia Areata is not fair

Name	
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the DG:	

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As a parent of a child who developed severe alopecia areata (alopecia universalis) at the age 12 years (a female) - this condition is devastating and takes away every shred of seld confidence - losing ones hair, including eyelashes and eyebrows has a huge psychological impact - and my daughter plunged into the depths of depression, she could not particpate in any sports - for fear of her wig falling off- and her social interactions were also severely affected with resultant behavioural and educational effects.
For NICE to imply that the cost of the drug does not justify the impact on the Quality of Life simply demonstrates the lack of understanding of this condition - and the fact that money is the key motivator for this decision.
My daughter has been on a JAK inhibitor for the past 23 months - and 5 months ago, she was finally able to go out without wearing a wig - as her hair has regrown to a length where she looks as if she has a short hairstyle. The regrowth of her hair has resulted in her self-confidence returning, and her depression has now lifted.
To see that NICE has not recommended that this drug be available on the NHS, is devastating.
Clearly, no one on this Committee has any empathy with regard to this condition.
In terms of the cost to the taxpayers, there would not be a massive amount of patients who would require the drug for this indication - and I am sure that a mechanism can be worked out where the drug could be prescribed by a Specialist Dermatologist - in the NHS - for this small group of patients whose lives would be dramatically improved by having this drug.
Therefore, I would like to appeal to the compassion and to the Common sense of the Committee members, to look beyond the 'dollar sign' and to actually look at the massive impact that this drug will have on patients' lives.

Dr [redacted]

Has all of the relevant evidence been taken into account?

No. The impact on mental health of patients with alopecia areata, and especially alopecia universalis, have not been taken into consideration. Alopecia areata affects several aspects of life, it causes identity crisis, work related issues, social anxiety, identity crisis, relationship difficulties etc. It is extremely challenging in situations like exercising, dating or meeting new people. Alopecia is more than just a cosmetic issue, it has daily psychological implications, causes higher rate or sickness and unemployment, increasing chances of depression and anxiety, as well as causing infections and makes it more difficult to regulate body temperature.

Are the recommendations sound and a suitable basis for guidance to the

Based on the overwhelming evidence provided by the pharmaceutical company and Alopecia UK refusing Ritlecitinib as a treatment for Alopecia Areata is not fair

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Name	
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the DG:	

Commenting as a family member of an alopecia sufferer.

I wish to state in the strongest terms about the mental health implications of alopecia. Its not simply solved by wearing a wig. My daughter's young adulthood has been destroyed. She has become socially isolated, has no career, and at age 30 still lives at home.

I could argue about the financial burden it places on me, but that is secondary to watching her ruined life.

She wants to use JAK inhibitors, but paying for it is a challenge. But if that makes the difference between her having the chance of a life, then it is worthwhile.

For other sufferers like her, it would have an impact on the economy. Better to have her working, making an income, paying taxes, and living, than rotting away, living off parents, family or the state, with degraded mental health.

Frankly, the NICE decision is degrading

Name	
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the DG:	

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I am saddened to see that yet again there is no recommendation from NICE for a treatment for Alopecia. Both Baricitinib and now Ritlecitinib have been denied despite being available for alopecia sufferers overseas. Most importantly they are FDA approved and thousands of people around the world are using it successfully. Alopecia is a chronic autoimmune disease that causes poor and severely reduced quality of life. I had Alopecia Universalis for 20 years. This had a serious impact on my mental health, I was no longer able to carry on work as a teacher and for many others it's a drain to NHS mental health services. It even leads to suicide. Alopecia also causes physical problems - lack of hair in the nose mean that there is constant rhinitis and inflammation. Lack of eyelashes and eyebrows cause dry eyes and infection. This is not a cosmetic problem. For the last 12 months I have had to pay for this treatment (JAKS) from a private dermatologist at some considerable personal cost. But it is worth it. I have full eyebrows, eyelashes, 80% scalp hair that is continuing to improve every month. My Q of L has improved significantly along with my general health. No eczema, rhinitis or other health issues that were costing the NHS money to treat. The Q of L standard that is used by NICE has been shown in the Baricitinib appeal to be woefully lacking in relevance for Alopecia sufferers. I urge you to put yourself in our shoes, or consider that a child or person in your family might be next to suffer with this life changing condition and approve this drug on the NHS. Thank you

Name	
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the DG:	
My son has alopecia universalis and there is currently NO effective treatment to encourage hair growth. Please do not underestimate the psychological effect this disease has. His mental heath has suffered considerably; at times he was suicidal. Please licence this treatment to be available on the NHS	

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Name	
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the DG:	

I have alopecia Totalis. This treatment would mean the world to me if it was available as I've had no success with anything else. Steroids, methexorate etc
My life has been turned upside down from February this year when I found my first patch to loosing every hair on my body within 2 months. I'm a 41 year old woman and feel like my identity has been taken from me. I don't want to get out of bed, every day!! I've had to stop working due to high anxiety. I don't want to leave the house. Yes I can wear a wig. There itchy, my scalp hurts. I can't have a "normal" relationship with my partner because most of the time I just want to die.

Name	
Notes	
Comments on the DG:	

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Yes, I believe that the quality-of-life measure used does not fully capture the views of people with alopecia. During my experience with this condition, I have experienced full regrowth with steroid injections, partial regrowth and losing most of my hair. Since losing my hair a year ago my quality of life has drastically decreased as has my confidence. If I completed a quality-of-life measure comparing this with a period of growth it would have been drastically different to my current quality of life. I engage with several social media groups used by thousands of people with alopecia which reflects similar views on this matter. For this reason, really question the validity of the tool used to assess quality of life in this group. I don't feel there is enough information about what stage of regrowth the individuals are at when assessed (this could make a huge difference, speaking from personal experience). I don't feel enough varied research including research with different quality of life measures has been carried out to state that it doesn't make enough difference. Who decides what is enough difference? Should it not be those who live with alopecia? I feel this group are not being fully considered. In addition, I don't believe enough notice has been given to

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charities who advocate on behalf of people with alopecia who have a lot of lived experience to draw upon.

Has all of the relevant evidence been taken into account?

I think more research with different quality of life measures should be used. Relying on one tool not designed specifically for people with alopecia is not grounds to discard the views of people living with the condition.

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

I don't think they reflect all circumstances for example I am currently taking methotrexate for my alopecia. It has not resulted in positive outcomes for me or many others (according to my dermatologist) and I feel awful on it. As a result of side effects, I have been making many more visits to my GP which I believe would outweigh the costs of having a more effective treatment. As treatment options are so limited I feel I have to persevere with an option that is not suitable for me or there is no other pathway. Wigs are not an option for me as I also have eczema and they irritate my scalp. Without other treatment options I don't feel I have any hope for the future.

Are the recommendations sound and a suitable basis for guidance to the

The recommendation are clear but I do not believe they reflect the views of health professionals that work daily with people with alopecia therefore I feel professionals would find it hard to recommend not having this treatment as their personal views differ.

Name	
Notes	
Comments on the DG:	

Alopecia is the only autoimmune disease where treatment is licensed but is not available on the NHS. Sufferers are simply left to accept their disease.

This article is now two years old and shows how out of touch NICE are with current thoughts.
"There are no FDA approved systemic treatments; therefore, an unmet need for safe, and effective treatments exists.
Ritlecitinib offers a novel mode of action, rapid onset, and the capacity for a superior safety profile over other JAK inhibitors. If approved, ritlecitinib will be widely prescribed by physicians overseeing the more severe AA patients for the foreseeable future."

[redacted]

Has all of the relevant evidence been taken into account? No

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Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence? No **Are the recommendations sound and a suitable basis for guidance to the NHS?** No

Name	
Notes	
Comments on the DG:	
Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation? There are several factors which the committee may wish to consider: o Women with autoimmune skin conditions including alopecia are at higher risk of spontaneous abortions than controls (Keum et al 2023, https://doi.org/10.1016/j.ajogmf.2023.101226). o People from black and ethnic minority backgrounds are significantly more likely to develop alopecia than those from a white background (Kang et al. 2023, https://doi.org/10.1016/j.jaad.2023.09.012) o Alopecia is commonly referred to in the literature as a 'disfiguring condition'. Disfigurement is protected under the UK Disability and Equality Act. **Has all of the relevant evidence been taken into account?** As a basic scientist with expertise in health economics, I understand the decision made by NICE based on the raw data presented. However, in my opinion, the nuances of this condition that are not well captured by EQ-5D (acknowledged by the committee in Section 3.13) have not received sufficient weighting in this decision. The impact on mental health is immense; recent data shows high levels of perceived stigmatisation, suicidal ideation and body dysmorphia in those with alopecia (Van Beugen et al. 2023 doi: 10.2340/actadv.v103.6485.) As a person living with Alopecia Universalis, I was pleased that the testimonies from patient and clinical experts were acknowledged and that the "profound impact on psychosocial health" and the lack of a standard care pathway or even access to treatment was recognised. However, I am disappointed that the decision has been made based on "most likely costs effectiveness" estimations, which in this instance, do not incorporate the mental health impacts of this condition and by nature, have a degree of uncertainty. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Again, I understand the cost effectiveness calculations undertaken based on the data provided. However, I believe the interpretations of clinical and	

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cost effectiveness in this instance are undervalued, in large part, because of the use of EQ-5D. Only one domain of EQ-5D (anxiety/depression) is readily applicable to people with severe forms of alopecia and those with anxiety/depression have been excluded from the ALLEGRO 2b/3 trial. Additionally, the study excluded those who had significant co-morbidities, which are common in alopecia. A recent meta-analysis shows that those with alopecia have 4-5 fold increased risk for lupus, metabolic syndrome and thyroid dysfunction (Ly et al. 2023 doi: 10.1007/s40257-023-00805-4)

Pfizer have presented vignettes to the committee to account for the lack of EQ-5D domains on social functioning, relationships, emotional impact, physical appearance or financial impact, which are relevant to the alopecia community. The committee note that the company employed “best practice” in the development of the vignettes, yet raised concerns around their validity including the lack of measures of other domains including mobility, which is already accounted for under EQ-5D. The NICE health technology evaluation manual notes that vignettes are acceptable if the evidence shows that EQ-5D is not appropriate. Yet, in this instance, they have not been considered. All real world data, including the Bewley poster cited by the EAG and a recent report on quality of life measures across five European countries (Vano-Galvan et al. 2023 doi: 10.1007/s13555-023-01057-0) show that the anxiety/depression domain of EQ-5D is most affected in alopecia. NICE have applied real world data that includes those with anxiety/depression to a trial that excludes these individuals in the calculation of cost effectiveness. This is not a fair comparison.

An additional limitation which is acknowledged by the committee is the lack of a standard care pathway for alopecia. In this case, best supportive care was defined as non-pharmacological interventions. As a person living with alopecia, the cost of best supportive care is considerable, and it is a cost I bear myself without support from the NHS. It is frustrating that had a standard care pathway been in place, the cost per QALY in this assessment could have been quite different.

Are the recommendations sound and a suitable basis for guidance to the

No. The limitations of the analysis of cost effectiveness are outlined above. The analysis is based on the committee’s preferred assumptions and although patient.

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Name	
Notes	
Comments on the DG:	

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

You are discriminating against Quality of Life and Equality of Life!!

Has all of the relevant evidence been taken into account?

Why put a cost on our lives! There are many areas that are funded with less severity as severe alopecia

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Why put a cost on our lives! There are many areas that are funded with less severity as severe alopecia

Are the recommendations sound and a suitable basis for guidance to the

There needs to be more.
Throughout the document it refers to the limited support and care given to sufferers of extreme alopecia, yet you feel there is nothing that can be done. The numbers are inconsistent in attendance of us sufferers with GP's, consultants and treatment because what is out there is not supporting us - evidence in itself together with the campaign from Alopecia UK. I myself, after initially receiving treatment (without success) have had to suffer alone and in silence! Every single day!! And you feel this treatment is not warranted!

Name	
Notes	
Comments on the DG:	

As a healthcare professional and having a daughter with alopecia you DO NOT recognise that losing hair can be extremely upsetting. For many people their hair is an important part of their identity and when people experience hair loss due to alopecia areata, it can significantly impact on how they feel about themselves, their mental wellbeing and affect their quality of life.
THAT WITHOUT THE COST OF MENTAL HEALTH THERAPY AND SUPPORT SHOULD BE ENOUGH TO PASS THIS DRUG FOR NHS USE.

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THE COMMITEE HAVE NO IDEA OF HOW THIS EFFECTS PEOPLE'S LIVES AND ARE THE ROOT CAUSE OF SUICIDE.
THINK OUTSIDE THE BOX FOR ONCE!

Name	
Notes	

Comments on the DG:

The committee papers included the experiences of two adults and there is a distinct lack of practical examples of where teenage children are being made to feel awkward, inadequate and shamed on a daily basis - just by navigating an average school day. The social exclusion by not feeling able to participate in contact sports for fear of ridicule not only has a short term impact on mental health but also a long term health and well being effect.

The issues raised around a loss of sex drive in older patients is not comparable to the fear of and expirenced shunning from the opposite sex purely because of their lack of hair (that could be treated).

I appreciated this is not the format that NICE wanted the responses in - and thankfully Alopecia UK and the dermatologist consultants will articulate the argument far greater than an extremely angry and frustrated father of a suffering teenage boy but the whole tone of this document is disgustingly void empathy or acknowledging the day the day challenges faced by children.

Everyday having to apply strong moisturising cream to keep the associated eczema at bay.

Applying fresh temporary eyebrow tattoos before school and hoping that they don’t peel and look ridiculous and therefore providing the school bullies further ammunition to poke fun and ridicule at.

Having to gain permission to wear a school cap around the school and in lessons to mask their bald heads. Which is a double edge sword as on the one hand marks them out as being different and therefore a target but the alternative is worse.

Being demanded to remove their school cap infront of crowds by teachers that are unaware of his condition and having to embarrassingly explain the reasons.

Occuring mid puberty when their bodies are changing only to reverse all the body hair, then having to expose this to changing rooms full of other boys.

Having to contend that being the ‘odd bald kid’ is going to impact opportunities with the opposite sex at the very time that testosterone is being to take effect.

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Viewing teenage girls with alopecia being able to mask their condition in public through the use of a wig and to the untrained eye they appear ‘normal’ whereas a teenage boy only has the option of wearing a baseball cap - which still exposes bald back and sides.

Not being able to remove a jumper without exposing yourself to others in public.

No longer being able to participate in swimming publicly despite having competed at a high level through fear.

Limiting life opportunities through avoidance of university.

Ultimately, and I apologise to adult sufferers, but the impact this condition has on teenage children comes with specific challenges that will affect their abilities to reach their full potential.

Once my son is 18 this opens up other opportunities e.g. microblading head tattoos that will be a potentially long term solution. Plus, at this age he will have grown in confidence - know who he is and will likely be able to ‘own’ his appearance at lot more.

A teenage boy’s years are the more crucial period to build confidence and to intentionally present a huge ‘potentially’ avoidable hurdle in their way is not a decision that I fear the committee has truly considered. If they had I feel the tone of the entire paper would read very differently.

Missing from the ‘equality’ discussion is the different current treatments for teenage boys versus girls. Currently there are no realistic options for teenage boy wigs

Name	
Notes	
Comments on the DG:	

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Stop hiding behind the quality of life when we already know this has great impacts on mental health, we feel discriminated against and we will be heard

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Name	
Notes	
Comments on the DG:	

It's heartbreaking to see on the Facebook groups how this is destroying lives and pushing people towards depression, anxiety, and even suicide. We need YOU to look beyond the financial aspect and prioritize the well-being of individuals.

Join the groups, check out the comments, and quit using quality of life as a shield to hide behind.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Stop hiding behind the quality of life when we already know this has great impacts on mental health, we feel discriminated against and we will be heard

Has all of the relevant evidence been taken into account? DEFINITELY NOT

Name	
Notes	
Comments on the DG:	

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

The recommendations don't take into account the outsized impact that Alopecia has on women and the resulting impact on their mental health which can include suicidal ideation and isolation from their pier group. Hair including eyebrows, eyelashes and bodily hair form a part of the female identity and they are constantly bombarded with images that reinforce models of acceptable appearance. This feeds into significant feelings of shame and the need to hide from society. Wigs and other types of artificial hair are not sufficient to have a significant impact on the impacts of this condition.

The outsized impact on women has been shown in studies including ' Psychology of Hair Loss Patients and Importance of Counseling' - Lakshyajit Dhami

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40% of women with alopecia have had marital problems as a consequence, and about 63% claim to have had career related problems - Hunt N, McHale S. Understanding alopecia. London: Sheldon, 2004

Although the impacts of alopecia have devastating impacts for people of all ages its is a particularly difficult condition for young people to cope with as it can lead to increased instances of bullying, social isolation and significant impacts on quality of life as they are unable to engage in activties which other children take for granted. This has been shown in the study - 'Alopecia Areata: Factors That Impact Children and Adolescents' Janice J wolf and Pamela Hudson Baker - Ritlecitinib is suitable for young people over the age of 12 but the study doesnt seem to give enough weight to the impact on this age group.

Has all of the relevant evidence been taken into account?

There isn't enough weight given to the amount of evidence of the impact of Alopecia on the mental health of sufferers that can be devastating and lead to significant amounts of NHS funding being spent on counselling, drugs to treat depression and other mental disorders and the cost of other associated disorders.

Alopecia can have serious psychosocial consequences, causing intense emotional suffering, and personal, social and work-related problems. Surveys have shown that around 40 per cent of women with alopecia have had marital problems, and around 63 per cent claimed to have career-related problems (Hunt & McHale, 2004).

Alopecia also leads to depression, anxiety and social phobia in sufferers.

increased prevalence rates of psychiatric disorders are associated with alopecia (Koo et al., 1994) suggesting that people with alopecia may be at higher risk for development of a major depressive episode, anxiety disorder, social phobia or paranoid disorder. Egele and Tauschke (1987) identified a group of alopecia patients with an ongoing feeling of loss, suggesting that for some individuals the process of coping with alopecia may be equated with the grieving process following
The recommendation is denying sufferers the only treatment that has has been shown in clinical trials to be effective. Without this there is no avenue of treatment and no hope for hair regrowth.

It also creates a two tier health care system where some can afford to fund the treatment privately and those on low/middle incomes cant get the treatment. I realise that NHS budgets are tight but it seams complete false economy not to fund a drug that would reduce pressure on budgets elsewhere particularly when it comes to mental health services which are under significant pressures.

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Personally the approval of this drug would significantly improve my daughters quality of life, significant funds are being spent by the NHS on drugs and counselling for her mental health, she has had to change schools, is unable to take part in activities that other children take for granted, while her friends have boyfriends she is unlikely to find a partner at this age accepting of her condition, she struggles with her identity, she struggles with feelings of shame and is embarrassed to go out and she has no hope as treatments are denied her. As carers it has had a significant impact on my wife, who is also now on anti depressants, it is a constant worry, its has had a significant impact on our quality of life.

It is my opinion that the quality of life tool 'EQ-5D' does not capture all the benefits of treatment for alopecia areata and that a condition-specific measure is needed, and that the lack of any other licensed treatments mean there are no direct comparators to assist in assessing cost-effectiveness. Whilst NICE continues to rely on 'EQ-5D' as a quality of life measure, and continues to compare the cost of new licensed treatments with 'no treatment at all', it feels that the answer is going to continue to be no.

Has all of the relevant evidence been taken into account?
There isn't enough weight given to the amount of evidence of the impact of Alopecia on the mental health of sufferers that can be devastating and lead to significant amounts of NHS funding being spent on counselling, drugs to treat depression and other mental disorders and the cost of other associated disorders.

Alopecia can have serious psychosocial consequences, causing intense emotional suffering, and personal, social and work-related problems. Surveys have shown that around 40 per cent of women with alopecia have had marital problems, and around 63 per cent claimed to have career-related problems (Hunt & McHale, 2004).

Alopecia also leads to depression, anxiety and social phobia in sufferers.

increased prevalence rates of psychiatric disorders are associated with alopecia (Koo et al., 1994) suggesting that people with alopecia may be at higher risk for development of a major depressive episode, anxiety disorder, social phobia or paranoid disorder. Egele and Tauschke (1987) identified a group of alopecia patients with an ongoing feeling of loss, suggesting that for some individuals the process of coping with alopecia may be equated with the grieving process following bereavement.

Furthermore, alopecia is a disfiguring disorder and therefore there are also issues relating to self and identity. The loss of hair, particularly the eyelashes and brows which help to define a person's face, means that a person looks very different. Hair loss may be seen as a failure to conform to the norms of physical appearance within society, a situation which has the

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potential to set people apart in their own estimation and in the estimation of others.

The impacts can be that people cant go outside or go to work for fear of being mocked. Women in particular described having problems, perhaps because of the importance of hair to a woman's notion of self and identity. Children and adolescents had problems, not just because they might be bullied at school, but because they are the ones going through the stages of establishing identity. If one's physical appearance changes abruptly at this point, then this can have catastrophic consequences.

These issues surrounding relationships demonstrate the importance of identity and selfhood, and how one's identity is not just personal, but bound up in the physical and social worlds. These findings are similar to those obtained for other types of fundamental appearance change or physical disfigurement, which often have profound psychosocial effects (e.g. Rumsey & Harcourt, 2005). Visible skin disorders having social anxiety and social avoidance implications simply because they are visible, irrespective of any physical problems associated with the disorder.

However sufferers of severe psoriasis are able to access JAK inhibitors on the NHS.

I have personal experience of the devastating impacts this condition has as my daughter suffers from Alopecia Universalis. She has been unable to attend school, is undergo counselling and is taking anti-depressants. She has lost her sense of self has been completely lost at a crucial time in her development into her teen years.

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

No - the impacts and costs to the NHS of Alopecia are being significantly underestimated. JAK inhibitors are currently the only effective treatment for this condition and additional weighting should be given to this fact. For sufferers there is a time limited window for treatment of up to 10 years in which hair regrowth can occur and makes the need for a treatment to be approved urgent.

The committee accepted that there were likely to be uncaptured benefits in any measure of health-related quality of life for severe alopecia areata. From my experience of being the parent of a child with Alopecia the report greatly underestimates the societal cost of this disease and the costs to the NHS.

It doesn't look at the costs that accrue to the carers of patients for whom the psychological impacts can be significant both to their mental health (with significant costs to the NHS) and their quality of life.

In the study there is mention that clinical experts said that for the average person with severe

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alopecia areata the true utility values might be higher than suggested by the vignette study. The report doesn't give enough weight to the severe impact of this condition of which there is evidence.

I fail to see how, when you look at the very significant costs to the NHS of treating both sufferers and carers that this doesn't represent value for money.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No the recommendations are not sound - they do not give sufficient weighting to the severe impacts of Alopecia on suffers and carers.

The recommendation is denying sufferers the only treatment that has has been shown in clinical trials to be effective. Without this there is no avenue of treatment and no hope for hair regrowth.

It also creates a two tier health care system where some can afford to fund the treatment privately and those on low/middle incomes cant get the treatment. I realise that NHS budgets are tight but it seams complete false economy not to fund a drug that would reduce pressure on budgets elsewhere particularly when it comes to mental health services which are under significant pressures.

Personally the approval of this drug would significantly improve my daughters quality of life, significant funds are being spent by the NHS on drugs and counselling for her mental health, she has had to change schools, is unable to take part in activities that other children take for granted, while her friends have boyfriends she is unlikely to find a partner at this age accepting of her condition, she struggles with her identity, she struggles with feelings of shame and is embarrassed to go out and she has no hope as treatments are denied her. As carers it has had a significant impact on my wife, who is also now on anti depressants, it is a constant worry, its has had a significant impact on our quality of life.

It is my opinion that the quality of life tool ‘EQ-5D’ does not capture all the benefits of treatment for alopecia areata and that a condition-specific measure is needed, and that the lack of any other licensed treatments mean there are no direct comparators to assist in assessing cost-effectiveness. Whilst NICE continues to rely on ‘EQ-5D’ as a quality of life measure, and continues to compare the cost of new licensed treatments with ‘no treatment at all’, it feels that the answer is going to continue to be no.

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Name	
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Comments on the DG:	

Hello. I can't comment on the above questions. What I can comment on is about life with alopecia.

I ask NICE to reconsider this decision to not approve Ritlexitinib for treating severe alopecia areata. This disease is devastating for those who have it. It affects every aspect of life - employment, appearance, socially and emotionally. When you have hair loss of any kind - especially if you are female, you are less likely to be considered for roles where you are 'customer-facing'; where you must be in the public eye, often get overlooked for promotions because it's thought that without hair, you don't look 'professional' or polished enough. You struggle to decide what to wear - without hair, your appearance is never complete. Some people create complicated hair styles to hide the bare patches, but then you are constantly worrying if it's moved, what happens on windy days or rainy days, will the product you use hold up?

Not having hair can also stop you from considering some career paths - performing, politician, sales, teaching - even being a server in a restaurant etc where you are in front of the public and appearance matters. 'Ugly' servers - especially women - don't get the job or don't get the same level of tips as 'pretty' servers do. Being sexy/sexual often includes having long shiny hair, not bald patches.

Wigs & attached hairpieces, yes, they are all available, but are expensive, time-consuming and add their own stresses - will they slip, fall apart before you can afford to get a new one, or get damaged so they don't look realistic? Often people will have to travel long distances to have these hair pieces maintained which adds to the cost - as well as being able to get time off work on a weekday. What the NHS is willing to pay for a wig is very low as well - a good wig costs thousands of pounds. You also can't do a lot of sports with a wig or hairpiece on as it can get damaged much more quickly.

Loss of confidence, pride in your own appearance, having people stare, make comments about your lack of hair, or automatically assume you have cancer is soul destroying. People hide away, stop working, socialising, and looking after their health because of alopecia areata. You don't want to be active when people star at the top of your head everywhere you go.

Having Ritlexitinib approved for use will be far cheaper for the NHS than not approving it as well - there will be cost savings for other illnesses and mental health issues. For those who find Ritlexitinib works, the boost in self-esteem, self-confidence, mental health is immeasurable. Being able to work, socialise and live life to the fullest can't be compared to the cost of this drug. It also boosts the UK Economy when more people are working, paying taxes, spending money.

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Pfizer will be able to continue their research for other drugs that can treat alopecia areata and other kinds of alopecia - this must start somewhere and this is the start with Ritlecitinib. Give people with alopecia areata a chance to try this drug. Regards [redacted]

Name	
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Comments on the DG:	
I do not believe the findings accurately reflect the potential positive effects of this drug in treating Alopecia. Beyond the obvious physical manifestation, the psychological impacts can be devastating on sufferers - as has been noted in the advice. The current "Best Supportive Care" does not effectively support the condition at all. As the father of a son with Alopecia, we have currently stopped all engagement with the NHS on the matter due to there being no suitable treatment offered. In the past we have seen GPs and Dermatologists, only to be told there is nothing that can be done. We have also had mental health support (for both our son and us as parents due to the stresses caused), and whilst this may help us to deal with things internally to a degree, it does not solve the issue of how others perceive and react to the condition. I would also argue that wigs as a supportive option are less suitable for males than females, and indeed not suitable for those who have dematological issues connected with the alopecia that makes them impossible to wear comfortably. As such, I find the costing in relation to supportive care to be null and void, as there really is no current suitable support offered. I have seen the positive effects of JAK inhibitors in people who are sourcing these through foreign markets, in many cases risking safety of what they are actually receiving. But they do it because both the cost and risk are outweighed by the benefits, physical and mental, that they derive from the treatment. As such, not giving NHS approval for this drug means that these risk levels will continue - but also only for those able to pay themselves. Surely the concept of the NHS is that this should not be the case for such a life changing condition. **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?**	

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I do believe that when current supportive care option of using wigs offers a lesser solution to male sufferers, and this context should be considered in the review.

Has all of the relevant evidence been taken into account?
I do believe that further insights into the mental health costs for those with the condition, as well as their families, deserves greater attention and implication. As mentioned in the comment, I also do not believe that the measure of supportive care is accurate - allowing people to give up on the NHS system because there isn't an answer does not mean the NHS has completed its responsibility of care. It is therefore natural that costs will be additional if there has not been an alternative in place.

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

Are the recommendations sound and a suitable basis for guidance to the

No. The system used is not fit for purpose with the variables chosen to measure the cost and effectiveness for this treatment.

Name	
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Comments on the DG:	
Not having access to treatment for Alopecia has a massive impact on the mental health of sufferers. All parts of life are impacted and the cost is very high both in terms of money and self worth. It seems very unfair that this is the second medication rejected, when similar auto immune illnesses are being treated on the NHS. Alopecia is much more than a cosmetic issue; this does not seem to be recognised. Be denying patients this medication, it feels like being dismissed yet again.	

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Comments on the DG:	
Her name is [redacted] she is 10 nearly 11, she has Alopecia Totallis, She got it in Covid lockdown ,[redacted] is having problems with people thinking she has cancer ,[redacted] thinks if she had cancer she could get treatment to make her better ,there is nothing to make her better NOT YET !! I'm her grandma I don't want to put statistics or numbers down I want to tell you children like her have no one to turn too no one to help ,I would give my body to help scientists NOW.. if it would help,I have hair Im 70 ! [redacted] has none, wigs don't help when at 10 she is constantly leared and stared at ..this is not just about her hair, its about mental health that comes with feeling different to all her friends and strangers ..having to explain why she has no hair ,Why reject JACS ?? when it mainly can help children like [redacted] the future of our	

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world ..This decision you have made will change our whole familys future with [redacted] she knows we love her but can't play God and help her but you can Help.... You are her GOD, from Grandma x

Name	
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Comments on the DG:	

Has all of the relevant evidence been taken into account?
I don't believe all of the relevant information and evidence has been taken into account, I don't believe proper and full consideration of patient experience

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

I continue to be shocked by the way in which success is measured in the case of severe alopecia areata treatment. There is currently no access to treatment for AA

Are the recommendations sound and a suitable basis for guidance to the

AA in the UK according to AUK and NICE data, surely the cost of treating these patients would return value in terms of quality of life and the ripple effect this has on friends, family, colleagues and the UK economy.
Finally, it seems to me that NICE continue to approach AA as a cosmetic issue and an one that can be treated with the use of cheap wigs. This is not an accurate analysis of AA and the experience of patients. JAKs are available and delivering positive results across Europe and the US, why are the UK so behind in terms of our understanding and respect of this condition?

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Comments on the DG:	

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Has all of the relevant evidence been taken into account?
I don't believe all of the relevant information and evidence has been taken into account, I don't believe proper and full consideration of patient experience

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Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

I continue to be shocked by the way in which success is measured in the case of severe alopecia areata treatment. There is currently no access to treatment for AA and therefore there is no comparator to consider and therefore no way to measure cost effectiveness. It continues to be more cost effective to reject new treatments and to continue to offer patients support from dermatology, mental health support and wigs.

Are the recommendations sound and a suitable basis for guidance to the

I don't believe that these recommendations are a suitable basis for guidance to the NHS. I have been living with severe AA since April 2021 and the only treatment offered to me on the NHS was a course of two immunosuppressants (Ciclosporin and Methotrexate) neither of which resulted in any re growth. My AA meant I had no hair at all on my body including inside my nose and ears which created additional challenges for me. I was offered mental health support as I was diagnosed with adjustment disorder due to the challenges of living with AA. The impact on my day to day life, my career and my family cannot be over stated. I have been miserable for more than two years.

In April 2023 I accessed JAK inhibitors privately and by September I began to experience re growth, I now have eyebrows, eyelashes, body hair including inside my nose and almost full re growth on my head. The impact this has had on my well being is incredible. I am anxious that things will regress if I cannot afford to continue accessing this medication privately, the thought of going back to life with no hair is devastating to me and I don't believe I would cope. There is no current treatment for severe AA however there is evidence of success through the use of JAKs, how are NICE using this information to arrive at a recommendation? It would seem that NICE is comparing apples with oranges here, is it simply easier not to recommend Ritlecitinib as there would be an increase in treatment costs compared to current costs? Has there been an assessment of actual costs of patients accessing NHS treatment for severe AA including all GP, dermatology and mental health support? Has there been an assessment of the impact on the economy from patients who can no longer function in society as a result of living with severe AA? And has this data been compared to the potential cost of treating patients with JAKs? There are under 200 people living with severe AA in the UK according to AUK and NICE data, surely the cost of treating these patients would return value in terms of quality of life and the ripple effect this has on friends, family, colleagues and the UK economy. Finally, it seems to me that NICE continue to approach AA as a cosmetic issue and an one that can be treated with the use of cheap wigs. This is not an accurate analysis of AA and the experience of patients. JAKs are available and delivering positive results across Europe and the US, why are the UK so behind in terms of our understanding and respect of this condition?

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Name	
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Comments on the DG:	

Has all the relevant evidence been taken into account?
There is not enough focus on the change to the quality of life to the patients.

Are the recommendations sound and a suitable basis for guidance to the NHS?
I am a sufferer of alopecia totalis. I think that this guidance undervalues and dismisses the devastating impact this condition has on sufferers. My experience since losing all of the hair on my head has been incredibly traumatic. Depression, anxiety, suicidal thoughts, I've had them all. I have had long periods of not working as a result of the psychological issues brought on by this. I have lost all confidence, it feels like I have lost everything. Yes, it's 'only hair' but it destroys you. It has taken everything from me. One of the hardest things to cope with is the feeling that no one thinks it's that big a deal. I understand that it can appear almost cosmetic and therefore less important. I also know that there are finite resources in the NHS. But this draft decision is yet another kick in the teeth.

It's hard to overstate how much a treatment like this would positively impact my quality of life. The potential to just be 'normal' again, not fearing that I will lose even more hair and just a bit of hope is huge. In real terms I would be able to walk into a room with confidence, I would not dread looking in the mirror, I would not wake up and check my body in fear for patches, I would be able to have physical relationships, I would regain my personality, I would smile more, I would not be the unwanted centre of attention, I would laugh more, I would spend less on hats.

I urge you to further consider the impact of this condition and the and the incredibly positive impact this drug will have on the patients.

Name	
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Comments on the DG:	

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation? No

Has all of the relevant evidence been taken into account? I'm unsure.

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Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
I don't believe so. I am using baricitinib privately after losing approximately 90% of the hair on my scalp as well as losing hair in my beard and on other parts of my body. I've been using this medication for approximately 6 weeks have regrowth in all areas. Admittedly the regrowth is short at the moment and is white in colour but this should turn to my normal colour within a matter of weeks or a couple of months.

I have been avoiding social engagements and face to face meetings at work because of my hair loss which has affected my confidence and mental health enormously. Already I now feel more comfortable in myself and social and work engagements and my confidence and general wellbeing will only improve further as my hair returns to its normal state.

Are the recommendations sound and a suitable basis for guidance to the NHS?
No, because it's as if Alopecia is a less important disease than other autoimmune diseases. You haven't factored in the psychological impact of this disease

I am a sufferer of alopecia totalis. I think that this guidance undervalues and dismisses the devastating impact this condition has on sufferers. My experience since

Name	
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Comments on the DG:	
No, because it's as if Alopecia is a less important disease than other autoimmune diseases. You haven't factored in the psychological impact of this disease I am a sufferer of alopecia totalis. I think that this guidance undervalues and dismisses the devastating impact this condition has on sufferers. My experience since	

Name	
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Comments on the DG:
Nice- I think you should get a better insight to the struggles of dealing with alopecia Physically and mentally It's a chronic inflammatory condition How suffers feel & what they would do for some eyelashes Let alone hair Eyelashes are very important to the human body I've lost my hair 45 times - Have you any idea how difficult this is- -yet these drugs are proven to help alopecia sufferers

Name	
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Comments on the DG:	
I have seen the committee guidance on using ritlecitinib in the NHS in England dated November 2023 and these are my views and comments on it. My overall view from reading the latest Committee guidance, and particularly section one entitled 'Why the committee made these recommendations', is that the Committee's initial recommendation is based upon financial considerations and that this appears to be the overriding factor in the committee makings its recommendation NOT to recommend ritlecitinib for treating severe alopecia areata in people 12 years and over. In my mind, this does not seem just or fair, and also makes any other submissions lesser or irrelevant to the committee when an overriding deciding factor appears to be a financial one. In effect, it would not matter whatever submissions might be advanced to the committee, if finance is the overriding factor in the overall decision making process. This point should be in the forefront of the mind of the Committee when a meeting is reconvened in January 2024. I am a professional woman, late 40's, and have been working since I was in my mid 20's, paying into the system each month I have worked. I try not to use the NHS unless absolutely necessary. I currently work part-time so do not earn a great deal and have always had long hair ever since I was a little girl. I was living a normal life when in July, for reasons unknown, I noticed large patches of hair missing from my scalp. I immediately went to my GP	

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as I was very concerned, who undertook blood tests - but these were all returned as normal. I was then referred to see a dermatologist – but at the time of writing I have not yet been seen by one and I have been told that there are likely no appointments available for 12 months (north London/Barnet). This in itself is wholly unacceptable and extremely disappointing, and I will try to follow this up to be seen sooner than this. As the weeks went on after July more hair continued to fall; so much so that I am now bald. I have gone from having beautiful 14-inch long brown hair to having virtually no hair on my scalp at all other than a few strands within 5 months. I have not been given any kind of treatment or suggestions by the NHS/my GP, nor been given any reference to any organisations for supportive care. I am extremely upset with the situation and cry most days about it. There is a great deal of societal emphasis placed on the beauty of hair and the confidence it gives. In effect I feel abandoned by the NHS. I have therefore been left by myself and the internet to try and understand why my hair might have fallen, to try and cope, and what treatments might be available. This was how I found the websites about ritlecitinib and the recent NICE (disappointing) draft guidance / recommendation.

Financial considerations / Price

This seems to be the most prominent aspect being taken into consideration by the Committee when making its recommendation. Yet it is difficult for any comments to be made on the financial position when the list price for the medication is not reported for confidential reasons. This is not even elaborated on in any way nor any comparisons or examples used to give a better understanding of what might be required or the costs involved.

Further, it is disappointing to note from the current recommendation that myself personally, and people like me, would not be a ‘cost effective use of NHS resources’ (3.20). I do not understand this based upon the Committees current reasonings. I and others would simply be denied the treatment via the NHS because it has not been made available to the NHS – and not by the degree of alopecia, or how I am affected, or my quality of life. This simply reiterates the point that the current recommendation is made purely on a financial basis and other considerations are dismissed. This to me seems to be unfair and generally discriminatory – against people with severe alopecia or for those without sufficient funds to pay for the treatment privately. Whilst this is not captured within the Equality Act 2010 as a distinctive group, it is reverse and indirect discrimination.

The Committee has admitted it has not been given all of the information it might need in order to make a further complete and considered recommendation, and openly admits that ‘The committee did not have a cost-effectiveness estimate that reflected all of its preferred assumptions’ (3.23). Despite this, the committee has concluded that ‘the analysis which most closely reflected these resulted in an ICER above the range that is normally considered a cost-effective use of NHS resources.’ This again reiterates the focus on the financial considerations applied in making the

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current recommendation and by inference dismisses all other considerations and submissions.

Treatments/options

Section 3 makes it clear that : ‘There are no licensed treatments available on the NHS for severe alopecia areata’ and that ‘there is no standard care for severe alopecia areata’. Further, at 3.11 that there is ‘no treatment pathway’. Given clear known conclusions on the current situation and treatments/support options available, I find it perverse that the committee have declined to recommend a new innovative and breakthrough therapy and treatment on the NHS that could really change and enhance people lives who are afflicted with severe alopecia. Currently it is simply being denied.

The recommendation also appears to be a blanket rejection, and does not mention any suitable criteria that might need to be applied and met before prescription of the mediation is given, and it is not even graded by severity or on a case-by case basis in any way.

It seems that there is a woeful lack of information and research into alopecia generally and historically, which is also apparent from the committees’ draft guidance. Given this, the Committee may never have all or any such relevant information about ‘quality of life’ improvement after taking the mediation before it unless further trials etc might be conducted in order to obtain and provide this information. It seems perfectly obvious that anyone who has their hair fall out and return substantially is going to have an improved and better quality of life than if it never returned. One could analyse the ‘quality of life’ in numerous ways and ergo it is not clear the benchmark the Committee is trying to reach on this aspect. Would it be judged on general happiness, confidence, self-worth, contentedness? The Committee is probably placing the wrong emphasis on this particular aspect, and should rather focus on the actual outcomes of hair regrowth after ritlecitinib is taken – which is, after all, the main purpose of the medication. The clinical trials for ritlecitinib showed positive results with a higher percentage of people experiencing hair regrowth.

The company’s vignettes

It is noted that the committee ‘concluded that the company had mostly followed best practice when doing the vignette study, although concerns remained around the validity of the results.’ These concerns are not elaborated upon at the end of this section, nor is there any indication that those concerns might be posed to the company for further detail or explanation. Has this now been done or will this be done before the next committee meeting in January 2024?

Conclusion

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The FDA approved ritlecitinib for use in June 2023. The European Commission approved ritlecitinib for use in September 2023. The Medicines and Healthcare products Regulatory Agency UK approved ritlecitinib for use in early November 2023. Without the Committees recommendation for England, the only people that would able to have access to ritlecitinib are those in private health care and those with money. That seems wrong and inequitable, and should not sit comfortably with the committee. Those who cannot easily afford the medication will simply be denied the potentially life changing treatment and will continue to suffer without real positive hope for a change to their alopecia. Time is of the essence and after 2 years the general view is that hair will not naturally regrow on its own without treatment.

I would urge the committee to reconsider the position and – when all necessary information (as best as possible) has been received and provided – would encourage the committee to recommend the application of using ritlecitinib in the NHS in England – if not wholesale, in some other way with perhaps criteria for use. If the Committee does NOT receive all of the necessary information it needs by the time of the next committee meeting, endeavours should be made to obtain and secure that information before making any further recommendation and a delay making any further recommendation if possible. If the information cannot be provided for lack of historical or trial research (which appears to be the case with alopecia), then serious consideration needs to be given to other factors advanced for those affected by severe alopecia . These other issues should be taken seriously and not be dismissed out of hand.

[redacted]
11 December 2023

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the

Yes, the current recommendation is seemingly made purely on a financial basis and other considerations are dismissed. This to me seems to be unfair and

Has all of the relevant evidence been taken into account? I'm unsure. No, it is clear that there is a great deal of information that has not been provided to the Committee and on some aspects may never be provided. See my main

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
No, as the Committee has not been provided with all the information it needs to make the decision and has openly admitted this**.**

Are the recommendations sound and a suitable basis for guidance to the NHS?

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No, they are currently discriminatory, and currently blanket denies anyone the treatment on the NHS. This appears to be inequitable.

Name	
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Comments on the DG:	
As a sufferer of severe Alopecia Areata, I would like to comment on the statement: 'Ritlecitinib may improve quality of life, but it is not clear by how much'. My quality of life and mental health would be drastically improved if there was a drug or any treatment that I could try to regrow my hair. I understand that we have to be very careful with how money is spent in the NHS but currently there is NOTHING for AA sufferers. Even if this could be offered to patients whose cases are severe on a limited trial basis and if it is deemed not effective the treatment would stop to save money. AA sufferers like myself do not seem to get any help at all from the NHS and because our illness is not properly understood, it seems it is merely pushed aside instead of drugs being tried/funded. Could it perhaps be offered as subsidised by the NHS to make it affordable for people to at least try? I know of people buying it at huge expense from abroad. I would not do this but at least if there was a system where the NHS could say 'this is safe and you can try it at a cost of £xx' we would at least feel as if our NHS cares and is trying to help us. Currently we feel abandoned which doesn't help with mental health. Thanks for the opportunity to comment. I hope you take my comments on board.	

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Comments on the DG:	
Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the I feel the decision was largely financial and I would ask why NICE approves therapies for obesity and smoking related diseases which are self-inflicted, and yet cant approve a therapy for a condition which is entirely random. **Has all of the relevant evidence been taken into account?** Psychological trauma in my opinion is understated in the report. Those (like my 26 year old daughter) who lost all body hair in around six months. We dealt with her trauma and as far as I can see NHS at best dealt with 10% of the psychological fallout,and yet NICE cites Wigs and Psychological support as being a preferred methodology, in reality it is very cheap wigs and next to no psychological support in most NHS trust areas.	

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Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Are the recommendations sound and a suitable basis for guidance to the NHS

Not really, in my view NHS consultants should have the option of at least a couple of months treatment to test efficacy.

Name	
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Comments on the DG:

It is with huge disappointment that I read of the negative response to approval of Ritlecitinib. I am a 60 year old woman, and lost all my hair over the last 12 months, following covid innoculations. It is the most distressing thing that can happen to a woman and I - along with many, many others - have been pinning our hopes on finally having something that could help our plight. The mental health impact of this disease knows no bounds. No hair, no eyebrows, no eyelashes - all the things that define us as "us", taken away. I know you will counter this by saying that wigs/false brows/lashes will "fix" it - but no, it does NOT fix it. The only thing that will "fix" it is hair regrowth. I have hardly left the house for the last 12 months - even with the aid of a wig - as self consciousness is taking me over. I have also been prescribed anti depressants. Wigs are uncomfortable, and no matter what anyone says, you DO notice it - especially with the lack of brows and lashes.

Anyone involved in the approval of this drug that does NOT suffer from severy alopecia areata, would be better off not being involved, because they can have absolutely no idea of the impact of this disease on people of any age. Finance should not come into it - there are many procedures which could be classed as cosmetic that are approved by NHS, so why should this be any different?

I see that the instances of alopecia areata have increased following covid jabs - and I feel angry about that. We did everything possible to help the whole country during that period - but pumping ourselves full of the jabs that may have helped with covid, but caused something totally different, and here we are having no support for having put ourselves through this distress.

No monetary value can be put in the mental health impact this has on me and many, many other people.

I hope that due consideration will be given to the sufferers of this severe disease, to give a better quality of life.

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Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the
I feel it is discriminating against Alopecia Areata sufferers, as a group.

Name	
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Comments on the DG:	
This is soo sad to hear. Having Alopecia universalis for now 2 years has had a huge impact on my health wellbeing, mental health , financial health also physical health. People see this as not medical condition however it is a medical condition called Autoimmune disease like many other Autoimmune diseases that exist. Not having any availability for any type treatment that clearly works is outstanding. The treatment that is available have very limited effect and clearly are not effective. Why can his medical condition not have any availability for treatment. Other Autoimmune disease that ate similar in health to Alopecia are allowed access This condition is debilitating, maybe not in way of mobility, pain, breathing. But it is a medical condition that causes medical concerns. Having one treatment should be allowed. Some conditions have many treatment available and this has not even one.	

Name	
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Comments on the DG:	
I am writing about the consideration of Ritlecitinib for the treatment of alopecia. My daughter lost all her hair aged 20. She was unable to continue her university degree due to the trauma and stress this caused. There have been numerous times I have been concerned that she might seriously harm herself due to not coping with the illness. She is now 50 and has never come to terms with her condition and I know never will. The impact of such a devastating illness on her sense of identity can never be reconciled. I have been repeatedly frustrated and distressed that the illness is viewed primarily in cosmetic terms and fails to acknowledge the true cost to sufferers' mental and physical state. The added issue now is the postcode	

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lottery relating to the very minimum financial contribution towards wigs. Again another failure to truly acknowledge the pain and suffering this condition causes. My daughter and others deserve recognition and support. There cannot be so many sufferers that the cost to the NHS would be excessive and I can assure you there would be savings in costs relating to mental health treatment such as anti-depressants or even admissions to mental health units. Please seriously consider the approval of this drug for the sake of the patients and as a cost-effective way of avoiding mental health treatments.

Name	
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Comments on the DG:	
I am a 41 year old woman suffering from severe alopecia arreata which began suddenly this year. The impact on my personal, professional and family life has been significant. As the committee itself notes, the effects of suffering from this devastating condition include psychological distress and have a major impact on day to day life. Alopecia is not a cosmetic issue and should not be treated like one. A wig is not a treatment, it is a way to mask the condition. Hair loss of this kind affects one's sense of identity and is a daily struggle. My sister and I both suffer from severe alopecia areata and are devastated by the committee's decision. The fact that a pharmaceutical response to this illness (in the absence of any other treatment) has been created is phenomenal, and it is with a sense of severe despondency and disbelief that I read the committee recommendation. It is hugely disappointing that such a narrow view of this illness has been taken, and the result appears to be partly due to the fact that the methodology for assessing whether it should be recommended for use by the NHS appears to be fatally flawed, without proper comparators. My alopecia has had an impact on my family and I am extremely disappointed in this result.	

Name	
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Comments on the DG:	
I am dismayed and angered by this decision to again reject another treatment for alopecia for use on the NHS and have once again felt let down and left hanging as there is currently still no effective treatments offered for alopecia universalis despite 2 treatment options both being deemed safe and effective by the MHRA. This disease, although does not impact physical health, has absolutely battered my mental health and has took complete control of my life to the point where I question my life every day, afraid of seeing people and have cut myself off from both family and friends which has absolutely killed me in one way. The only thing that has kept me going is the thought that hopefully one day soon that I would be able to receive a treatment of this kind to hopefully get my life back and start living again instead of becoming the recluse that I now am, and to consistently have these kinds of treatment options rejected over and over is becoming very	

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difficult to take and seems people like me and others with this condition are just left hung out to dry and as though it is not a serious enough condition to be worthy of any help which I find completely wrong and unfair. I just wish you would understand how much this would mean to people to be able to be given a chance to have this treatment option as we at a disadvantage enough as it is with no options of treatment, I have recently in the past 8 months had appointments with dermatologists, which took an endless amount of time just to get an appointment and then to be messed around with my first appointment and then the follow up appointment being pointless as the immunosuppressant I was told I could try from the first appointment not being offered so I came away no better off and feeling extremely alone and depressed at the thought of never having a treatment option. I really wish you could put yourself in our shoes and understand how much of a positive effect this would have on our mental well-being to even just be able to even have the chance of trying this treatment, I'm even at the stage now where any regrowth such as my eyebrows or beard would help me to feel a lot better within myself and have an extremely positive effect on my life. I also feel that if I was allowed to have this treatment and if it did not work for me then that would still have a positive effect and feel that I would then be able to finally accept that this a condition I will have to live with but knowing that there are treatment options out there that could genuinely be effective and that the only things that are preventing me from having this treatment are of my control I feel that I'm never going to come to a stage where I accept this and find a way to move on with my life. If this treatment was to be approved and was to work successfully for me then I could not put it into words how much this would change my life and allow me to get back to things that I should be doing for someone of my age such as going on holiday, having nights out with my mates and even something as simple as not having to feel embarrassed of myself for just being out in public and having the feeling that everyone is looking at me, it is the thought of that alone that is seeing me through these really dark times of my life. I really strongly urge and plead with you to reconsider the recommendations you have put forward and allow people like me the opportunity to receive this treatment because this is something that could be life changing and show the alopecia community which has been neglected for what seems like forever that finally after all this time there is some help for us and to be recognized what a damaging condition this has on our mental health. **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the** I feel it is discriminating against Alopecia Areata sufferers, as a group. **Are the recommendations sound and a suitable basis for guidance to the**

Name	

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Comments on the DG:	

Children are affected. We should be protecting them from the impact. Easier to disguise in girls. Culturally hair loss is far more impactive as is symbolic.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the

Has all of the relevant evidence been taken into account? I'm unsure. No it was proven from Baracitinib appeal that the quality of life index is not fit for purpose for any skin complaint. This is readily accepted by nice as it was for previous approved skin complaint treatments. Yet nice have used this index again to judge Ritlicitinib. Previously practitioner evidence has been accepted for other drugs over the quality of life index which relates to mobility etc and is not relevant at all to AA.

Mental health cost both to individual, surrounding family and thus NHS not measured or considered!

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No as most AA patients don't treat as it is pointless existing treatment simply doesn't work and can cause other issues like thinning of skin/skin cancer. Therefore, benefit to cost ratio not relevant. This treatment has a good chance of working to some degree example restoration of eyebrows and eyelashes making different appearance less obvious/impactive. Thus a degree of mental health improvement.

Are the recommendations sound and a suitable basis for guidance to the

No as above quality of life index not fit for purpose for AA.

Impact of mental health and associated treatment not measured.

Consideration of other treatment for cost analysis not relevant as no other treatment works so pointless. Ask a Dermatologist!!!!

NICE/NHS approved Baracitinib for non-AA conditions. Also approved other skin condition treatments based on Clinician evidence not quality of life index so there is a precedent ignored in the case of AA treatment. This is both unjust and unfair. Ritlicitinib is a treatment that works. Comparing both these drugs to no treatment (As other treatment is worthless) is a nonsense. Treatment for other appearance driven issues is readily available via NHS. Drug addicts, smokers, overweight people are readily treated via the NHS, yet the mental health of AA patients ignored.

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Name	
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Comments on the DG:	
Is this reasonable guidance from the NHS' - the answer is NO! Patients with Alopecia deserve a better quality of life and lowering mental health issues associated with hair loss, which would save the nhs money in that area!	

Name	
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Comments on the DG:	
Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation? Testing and study to be conducted within a certain timeframe of the condition as this would determine a more accurate assessment. **Has all of the relevant evidence been taken into account?** I'm unsure. Age and length of condition has not been determined within the study. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** The cost effectiveness is clearly inaccurate given that there is no evidence of any other pharmaceutical provider and is purely based off 1 providers price. **Are the recommendations sound and a suitable basis for guidance to the NHS.** I do not agree that the recommendations are sound and a suitable basis for guidance to the NHS	
Name	

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Notes	
Comments on the DG:	
Alopecia areata (and particularly Alopecia Totalis and Alopecia Universalis) is a disability and as such NICE are discrimating against people with these conditions. **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?** Yes NICE has discriminated against people with Alopecia areata which is a disability with no treatment options. **Has all of the relevant evidence been taken into account?** I'm unsure. I don't believe that the health aspects of having severe Alopecia have been taken fully into account. People who have Alopecia Totalis or Universalis and are by necessity wig wearers are unlikely to participate in sport or fitness regimes. You can't participate in contact sports or swim if you wear a wig. This has a long-term effect on physical health. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** **Are the recommendations sound and a suitable basis for guidance to the NHS** No I think that the true impact of Alopecia areata on an individual has not been properly considered.	

Name	
Notes	
Comments on the DG:	
I think NICE should be nice and include this alopecia medication, which could have a fundamental impact on many quality of life. Perhaps NICE should work closer with Pfizer to reduce drugs costs to the NHS. Thank you.	

Name	
Notes	
Comments on the DG:	
Dear Sir/Madam, I am writing to you to express my personal concerns in response to this draft guidance for the use of the drug Ritlecitinib within the NHS. I want to provide further personal experience on your ‘Best supportive care’ understanding and current practices.	

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I am a 26-year-old British woman with Alopecia Universalis. I have lived with the condition for nearly 3 years now, after this was triggered very shortly after having the Pfizer branded vaccine for COVID-19 (I believe there are early discussions on this potential correlation).

Human Hair wigs are now in short supply, meaning the cost of the average wig is rising each year. Every year I will spend thousands of pounds, which is astronomical money from a small single person's salary on items such as 1/2 wigs per year (as these normally need to be replaced once per year), maintenance, time off and travel for medical appointments, products and treatments for my head and skin. I suffer with eczema and repetitive skin irritation from constant wig use as well.

My local borough in London will only contribute £100 per year towards the cost of a new wig, thus proving your comments on 'varying rates across health states and arms' comments. The financial strain on me has been astronomical, adding to my deteriorated mental health.

I have also had to wait for a long time for any mental health support. There is a lack of tailored psychological support around the issue of the condition of Alopecia. I have had 'generic' CBT therapy, and whereby my therapist will provide support for issues around suicidal thoughts, anxiety, and depression, but nothing specifically for Alopecia.

I feel it is a 'Postcode lottery' when it comes to medical, psychological, and financial help for Alopecia depending where you are in the UK support both on the NHS and privately vary astronomically. I have suffered with suicidal thoughts due to my condition.
I have exhausted limited treatment options available currently. I have tried Methotrexate and Ciclosporin, both already having proven low success rates, we need more options.

I strongly believe that JAK inhibitors will give me a better quality of life, with less financial and psychological strain, meaning I may not need to access as much mental health support on the NHS.

These examples affect every aspect of my life, from everyday relationships with family and friends, to working to be able to fund a condition I cannot control.

I would be happy to provide further information on this matter if required, and I look forward to reading your final guidance in due course.

Thank you for considering my comments.

Yours faithfully,

[redacted]

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Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Has all of the relevant evidence been taken into account?

I'm unsure.
Questions around whether Pfizer's vaccine for COVID-19 should be taken into account as well. I understand the research here is limited, but these can correlate.

Secondly, referring to your 'best supportive care' points, I think the cost of wigs should be considered, and the lack of financial support in this area. For example, my local borough in London will only contribute £100 per year towards the cost of a new wig, thus proving your comments on ‘varying rates across health states and arms’ comments.

A lack of mental health support and long waiting lists in the UK should be considered. There is a lack of tailored psychological support around the issue of the condition of Alopecia. I have had ‘generic’ CBT therapy for suicidal thoughts, anxiety, and depression, caused by having Alopecia, wearing wigs which has caused me to lose my identity and dignity as a person.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
Current treatment options for severe levels of Alopecia such as Methotrexate and Ciclosporin have low success rates, and are costly to the NHS. The options are

Name	[redacted]
Notes	
Comments on the DG:	
Please NICE I urge you to reconsider before inevitably posting your guidance not recommending ritlecitinib for severe alopecia. I have alopecia universalis, it has **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?** **Has all of the relevant evidence been taken into account?** I'm unsure.	

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Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Are the recommendations sound and a suitable basis for guidance to the

Name	[redacted]
Notes	
Comments on the DG:	

Please NICE I urge you to reconsider before inevitably posting your guidance not recommending ritlecitinib for severe alopecia. I have alopecia universalis, it has

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Has all of the relevant evidence been taken into account? I'm unsure.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Are the recommendations sound and a suitable basis for guidance to the

Name	
Notes	
Comments on the DG:	

How can it be said that they are unsure on how much improvement to quality of life this would make. I have Alopecia Universalis and have felt suicidal many times! My quality of life would be massively improved.

This drug would make such a massive difference to many people. Young and older, we are over looked at every step.

I lost every hair on my body in the space of 3 weeks. It has left me agoraphobic, suffering with deep depression, suicidal thoughts and severe anxiety

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This drug would be life changing for so many people. Please can someone give sufferers of Alopecia a break, regardless of what Alopecia they have and regardless of their age! It's a postcode lottery for us as it is, I have been on oral steroids for 2 years and they are making me ill but the hope they may work one day keep me taking them. It's not just hair, it's part of us, and without we feel vulnerable and isolated.
Name: [redacted]
Notes
Comments on the DG:
I'm a 32 year old female. I have alopecia universalis. I have tried treatments currently available through the nhs, such as contact immunotherapy, they don't work. I have spent thousands of pounds over the last 10 years on wigs that look realistic enough to wear in public. However my confidence and mental health are at an all time low, I don't work and have no social life, I have shut myself away. I don't think it's an exaggeration to say access to treatment, that works, through the NHS would be life changing for so many people in the same situation. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Comparing the cost of a new licensed treatment to no treatment at all is always going to result in rejection. Please reconsider.

Name: Rita Davies
Notes
Comments on the DG:
Are there any aspects of the recommendations that need consideration to ensure we avoid unlawful discrimination against any group of people on the against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation? As an Alopecia sufferer..I am annoyed that the condition is seen by NICE to be cosmetic...it definitely is not My mental health has suffered so much...to the point that 5yrs ago I was planning my suicide **Has all of the relevant evidence been taken into account?** Definitely not..Alopecia is not just the loss of hair...without nasal hair..I have had numerous URTI and without eyebrows and eyelashes...frequent eye infections

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Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
No...I feel very strongly that we are the forgotten victims of this horrid disease that zaps your confidence and steals your identity I have been on antidepressants for the last 5years
I was an NHS nurse for 45years before I retired and am very annoyed that I now have to buy JAKS from India out of my NHS pension Please reconsider your decision,consider how this condition impacts on our lives.....I'm an older lady but I'm not just thinking about myself but the younger patients who have their whole life ahead of them
Have you actually interviewed people with alopecia to have understanding of the impact it causes on our day to day life?

Are the recommendations sound and a suitable basis for guidance to the NHS?
No...you need to consider our mental health and not see it as cosmetic

Name: Sam Janssen
Notes
Comments on the DG:

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

As a sufferer for the past 4 years, I now look like your grandad, completely bald on top with a bit of hair on the back and sides. As a middle aged woman this is a pretty devastating disease to live and come to terms with. My quality of life, and thousands of others would be improved if there were access to this treatment option.

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Name:
Notes
Comments on the DG:

Ritlecitinib may improve quality of life, but it is not clear by how much.

Going from suicidal/depressed to feeling like yourself again because your hair has grown back, owing to taking Ritlecitinib, is a massive improvement in quality of life. How can a questionnaire asking whether you can wash yourself or dress yourself have any adequate meaning to the quality of life endured when you have Alopecia? How can a questionnaire, where you can suggest you're feeling suicidal, still give you a high mark on the quality of life score, have any suitable meaning to the matter in question?

The most likely cost-effectiveness estimates for ritlecitinib are higher than what NICE normally considers an acceptable use of NHS resources. So, ritlecitinib is not recommended.

Has NICE considered how much of NHS resources would be saved by allowing patients to use Ritlecitinib? The cost burden of NHS mental health services, wig costs

Effects on quality of life
They said that it can lead to social exclusion and can limit career progression or education because of an inability to fully participate in societ:

From my personal experience, I can say that I feel that the cost of my alopecia and depression experience has a much higher cost to society, than if I was to receive

They emphasised that alopecia areata is not a cosmetic issue:
Correct. Alopecia is an autoimmune disease. People with other autoimmune diseases are given treatment (including JAK inhibitors, which I think is discriminatory.

Treatment options
The patient experts said that many people with the condition do not have any treatments:
I personally have not been offered any treatments. No treatment in a decade of suffering with Alopecia. Not even mental health treatment was offered. That's why the cost the NHS is currently so low - it's because alopecia sufferers are fobbed off and told to go away and put up with the condition.

The patient experts explained that the availability of wigs varies regionally and that those offered by the NHS are often unsuitable:
This also doesn't cover the fact that some people don't want to wear wigs, either because they look unrealistic or because they're hot and

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uncomfortable to wear. Why treat the symptom of Alopecia - by hiding appearances - when the cause of it could be treated, by using Ritlecitinib.

People with alopecia areata often spend their own money on wigs and other appearance-altering treatments such as microblading:

If NICE is not going to recommend that the NHS offers treatment for the CAUSE of Alopecia, they should absolutely be recommending that more funding is spent on "appearance-altering treatments". But that won't be done either. So it'll stay as it currently stands, Alopecia sufferers can't be treated and they also can't afford the appearance-altering treatments that would go some way to making them feel like themselves again. This decision on Ritlecitinib has the ability to strip people of their dignity, or give them hope for their future.

Has all of the relevant evidence been taken into account?
No. By only using the EQ-5D quality of life measure, it is impossible to truly grasp how much of an improvement to quality of life it would be to take Ritlecitinib.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
No. It is unacceptable to suggest that the cost of Ritlecitinib vs. Costs currently being spent on alopecia is an acceptable way of comparing costs. Currently, a lot of costs are paid by the patient privately, because the NHS just won't cover costs, so of course NHS costs are currently low. Alopecia sufferers tend to pay for their own wigs, eyebrow treatments, mental health therapy, because there is little to no NHS provision.

Are the recommendations sound and a suitable basis for guidance to the NHS.
No. How can it be a suitable basis for guidance to the NHS when Alopecia itself isn't treated with the seriousness is deserves? More needs to be made about the fact that Alopecia is an autoimmune disease - and quite often where there is one, there are more. One autoimmune condition can trigger another, and then that means the NHS has to investigate and treat more. The NHS needs to recognise that Alopecia is a serious condition, not a cosmetic condition, but a physical AND mental health condition.

Name	
Notes	
Comments on the DG:	
My 14-year-old daughter has alopecia areata. We are a family where auto immune conditions is high where I have rheumatoid arthritis and my older daughter of 18 years has lupus. Having a drug treatment pathway with options to try drugs that can treat the symptoms of both my and my and my 18-year-old conditions has been hugely beneficial in the long term for both physically and mentally. Alopecia areata needs this drug pathway to give people the options to find a drug that can be beneficial to their condition.	

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Wigs and cover ups are temporary and masking and has an adverse impact on the patient and the NHS with underlying mental health conditions festering. JAK inhibitors can be very successful, improves quality of life and in turn give people the opportunity to live healthy normal lives and limits the strain on an already strained NHS. Auto immune conditions are very specific to the person and having drug options means that it will work for some patients if not many and in turn will have a positive impact on health overall.

Name	
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Comments on the DG:	
There's no costly comparator but deemed not cost effective. It may be my of knowledge depth, but as a Alopecia Areata patient this confuses me.	

Name	
Notes	
Comments on the DG:	
This is a very disappointing decision for anyone with Alopecia. Please reconsider. The hope that this treatment is giving sufferers has been taken away. My son and daughter both suffer from AA - my daughter's is very severe. Over the past 15 years we have struggled with various treatments that have been unsuccessful. We have been waiting in hope for JAK inhibitors to become available in what was seen as the first hope we have had in a long time. The mental health aspects of this condition should not be underestimated. Teenage boys and girls are so conscious of their appearance and just want to fit in. They became depressed, tearful and anxious. They have had comments made by strangers and their peers. It isn't enough to be handed a prescription for a wig and to be told there's nothing can be done - the postcode lottery for wigs is another argument! My daughter is now sourcing JAK inhibitors from abroad and has great regrowth after only 10 months. For the first time she has hope - her depression and anxiety has lifted. She is no longer taking antidepressants. She is like a different girl. We are in the position to have been able to source private appointments and the medication but what about those who can't afford to do that for their children? This is an absolute shame and it disgusts me about how people with AA are treated. If this was a self inflicted illness through obesity or smoking, the NHS would pay for their treatment. The difference that taking JAK inhibitors has made to my daughter is huge! She has now got eyebrows to stop perspiration running into her eyes. She has most of her eyelashes which has helped during the hayfever season. Her mental health has improved tenfold- saving the NHS money in medication and CBT. She finally has hope of being able to swim again without having to worry about her wig coming off. She was a training to be a	

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professional dancer- impossible to do various show hairstyles for productions. She now has the hope of soon being like just one of her friends.
I realise that it is difficult to show how quality of life is improved by these drugs but it's the little things that most people take for granted that makes such a difference to people with AA. These little things cause additional stress - the self image and mental health link is huge. Please reconsider your decision for the sake of all the AA community in the U.K. . Many thanks, [redacted]

Name	
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Comments on the DG:	

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

This consultation discriminates against those with alopecia because it fails to recognise the full lasting negative impact of this condition which it then claims is too costly to fund by the NHS.

This argument is completely flawed because you are refusing to disclose the cost of treatment. The cost of treatment needs to be disclosed in order to have an open procedure for assessing cost/benefit.

Alopecia is a life-changing condition and should be classed as such. Treatments such as this are already prescribed on the NHS for eczema. Thousands of dogs are prescribed Jak Inhibitors across the country. The alopecia community is being valued lower than a dog life.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
No. NICE have failed to support their cost effectiveness argument because you are refusing to disclose the price of treatment. You cannot argue on cost and value

Are the recommendations sound and a suitable basis for guidance to the NHS?

The best scientists in the world strove to do good because they also had humanity - where is your humanity?

Shame on you for supporting a system for undervaluing our daughter's life (at an undisclosed amount which we are not deemed worthy to be given).

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And shame on you for undervaluing and misrepresenting the suffering of the alopecia community in the UK. You are an absolute disgrace.

Try putting yourself in our daughter's shoes for one moment, living her life, then tell us it has no value.

Name	[redacted]
Notes	
Comments on the DG:	

Furthermore, the absence of licensed treatments for severe alopecia areata on the NHS leaves individuals with limited options. It is unacceptable that individuals facing such challenges can only access novel treatments if they can afford to purchase medication privately. This creates an alarming disparity where those reliant on NHS treatment are unfairly deprived of potential solutions.

The situation becomes even more disgraceful when considering the profound impact on the quality of life that alopecia areata can cause. NICE's decision seems to perpetuate an inequitable system, where only those with the financial means can avail themselves of innovative treatments. Families and individuals grappling with alopecia areata should not have to endure this added burden of financial strain.

In the interest of fairness, inclusivity, and compassion, it is crucial for NICE to reconsider its stance and prioritise the well-being of those affected by severe alopecia areata. Access to innovative treatments should not be contingent on one's financial capacity; it is a matter of basic human rights and dignity.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Has all of the relevant evidence been taken into account?
The decision underscores and need a condition-specific measure.

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Name	
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Comments on the DG:	

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Alopecia can be considered a severely disfiguring condition. Disfigurement is protected under the UK Disability and Equality Act.

People from black and ethnic minority backgrounds are significantly more likely to develop alopecia than those from a white background. It is 3 times more prevalent in South Asian communities.

Has all of the relevant evidence been taken into account?
If I have reviewed the report correctly, you have heard the voices of the patient and clinical experts and the vignettes provided by Pfizer. Despite the gripping.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I do not know I am not an expert in this.

Are the recommendations sound and a suitable basis for guidance to the
No, patients with alopecia deserve much more care. We are abandoned by the NHS. By not approving JAKS, NICE is perpetuating a socioeconomic divide for patients with alopecia, because paying privately is out of the reach of most people. This decision has a larger weighted impact on those who are least likely to be referred to dermatology (non-white people), and those who are poorest and will spend more of the income on this.

Adults and children are suffering and in the worst cases, some are losing their lives as a result of alopecia. I am aghast that with two innovative licensed treatments, those people cannot access care. How dare you presume to say you understand this and then not approve.

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Name	
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Comments on the DG:	
My granddaughter who is 10 years old and had alopecia totallis since the age of 7, she has been constantly going in and out of hospital, for all sorts of tests ,including taking of bloods etc,every time expecting to have good news about treatment to help,only to be let down time and again, each time going through bouts of depression for days on end, she is now saying that she can't cope with anymore tests,only to be told there is no help. She has been on numerous diets to try to help her immune system also to no avail. As a grandparent I am extremely concerned about Ella's mental health, she knows there is a jacs treatment that works but as she is 10 years old cannot receive the treatment, she says that if she had cancer and no hair at least she could receive treatment to make her better, how are we as grandparents to explain when there is treatment available to people with asthma that she can't have any. Surely the monetary cost does not override the mental cost to a young child.	

Ritlecitinib for treating severe alopecia areata in people 12 years and over. A Single Technology Appraisal

Second addendum: Critique of company's submission following the first committee meeting

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1. Introduction

In September 2023 following the first committee meeting, NICE wrote to the company requesting that they provide additional information to aid the committee's decision making. This included a request that the company provide updated cost-effectiveness analyses incorporating the committee's preferred assumptions. In October 2023, in response to this request, the company provided a set of updated cost-effectiveness analyses which incorporated a revised patient access scheme (PAS) discount. NICE has asked the EAG to verify the updated results provided by the company. In this second addendum to the EAG report, the EAG has assessed whether the company's updated analyses are consistent with the committee's preferences and whether the updated PAS has been correctly incorporated.

In its letter to the company after the first committee meeting, NICE also requested that the company provide further EQ-5D follow-up data from the ALLEGRO clinical trials and a scenario analysis incorporating this evidence within the economic analysis. The company provided the additional EQ-5D follow-up data requested but it has not incorporated these data into its updated economic analysis. NICE has advised the EAG that it does not require a critique of the additional EQ-5D data at this time. NICE also requested further information from the company regarding the appropriateness of the EQ-5D and other generic and condition-specific quality of life measures in alopecia areata. In response the company stated that, *"no further evidence can be provided beyond that already in the Company submission."* Therefore, this second addendum focuses on validating the economic analyses provided by the company. This second addendum should be read in conjunction with the EAG report and the first addendum which provided a critique of the company's response to technical engagement.

All results presented in this document include the revised PAS discount which reduces the cost per pack of 30 capsules from a list price of £[redacted] to £[redacted], equivalent to a simple discount of [redacted]% on the list price.

2. Summary of company's updated cost-effectiveness analysis

The company has made three changes to their previous base case as follows:

- using utility values for each health state mapped from the mild, moderate and severe disease utility values from Bewley *et al.*[1]
- using the average transitions in health states over the final year for which data was available to estimate the long-term treatment effect
- using the exponential model to extrapolate time to treatment stopping.

These changes are consistent with the committee's preferences as outlined in the letter from NICE to the company. These changes also bring the analyses presented by the company in-line with the EAG's base case following technical engagement (see EAG report addendum 1).

The committee also requested that the company presented results as follows:

- weighting the average outcomes for young people and adults in the model separately
- weighting the incremental cost effectiveness ratio (ICER) according to the proportion expected to have alopecia totalis (AT) or alopecia universalis (AU) in clinical practice (9.52%).

In order to facilitate the presentation of ICERs based on weighted outcomes across age categories (young people and adults), NICE requested that the company provide an estimate of the proportion of people with severe alopecia areata in clinical practice who are young people and scenarios to show the impact of different estimates of this proportion on the ICER. The company provided one estimate of this proportion, based on prevalence data from the Oxford-Royal College of General Practitioners (RCGP) database. The company reports that according to this database, the prevalence of AA is [redacted] among 12-17 year olds and 0.58% among adults. The company has combined this with demographic data for England from the Office of National Statistics (ONS),[2] to estimate that 4.91% of people with AA are aged 12-17 years (see Company response, Table 6). This proportion has been used to generate the company's results when weighting average outcomes across age groups and no other values have been explored by the company in scenario analyses.

3. EAG's critique of the updated economic analyses

The EAG has been able to verify the prevalence estimates of 0.58% for AA in adults from a publication describing an analysis the Oxford-RCGP Research and Surveillance Centre (RSC) network database.[3] However, this paper does not report the prevalence for children or specifically for the 12-17 years old age group. It does report the incidence of AA per 1000 person-years by 5-year age bands, but further calculations would be required to estimate the prevalence for 12-17 years olds. The company's citation is for the database rather than a particular publication, and therefore it is possible that this estimate was requested directly from the database owners,[4] but the EAG cannot independently verify the estimate. The EAG also notes that the prevalence estimates provided by the company are for AA and not severe AA. Therefore, the company's analysis is implicitly assuming that the proportion of patients with severe AA does not differ between young people and adults. The EAG therefore considers that there remains some uncertainty regarding the proportion of people with severe AA who are young people aged 12-17 years. Therefore, the EAG has provided a threshold analysis which explores changing the proportion of people with severe AA who are young people until the deterministic ICER reaches a threshold of £30,000 per QALY.

4. Results of the EAG's verification and additional analyses

The EAG verified that the changes made to the model were consistent with the committee's preferences, as stated by NICE in the letter to the company. They EAG also verified that the company's updated analyses were also consistent with the EAG's base case after technical engagement. The EAG has been able to reproduce the results provided by the company with only minor differences identified that may reflect either typographical errors in the reporting or small differences in the rounding at various stages in the calculation of results based on weighted averages. The results generated by the EAG are provided in Tables 1 and 2 with footnotes indicating any minor discrepancies identified. The deterministic ICER across the whole cohort ranges from £25,892 per QALY when calculating a weighted average across those with and without AT/AU, to £29,986 per QALY when calculating a weighted average across age subgroups and assuming that 4.91% of the eligible population are young people aged 12-17 years.

The EAG's threshold analysis identified that only a small decrease in the proportion of patients with severe AA who are young people (aged 12-17 years) from 4.91% to 4.65% is required to achieve an ICER of £30,000 in the whole population, when using weighted average outcomes across adults and young people. However, the EAG notes even though the cost-effectiveness is more favourable for adolescents compared to adults, the deterministic ICER for adults is £30,249 per QALY, and this provides an upper limit to the deterministic ICER for the eligible population, despite the uncertainty regarding the proportion who are young people.

The EAG has also re-run the PSA for each age subgroup and results based on average outcomes across 10,000 samples are provided in Table 3. (The EAG was unable to run the PSA for the subgroups with and without AT/AU.) In each age subgroup, the probabilistic ICER is within 5% of the deterministic ICER. For the adult cohort, the mean ICER was £31,399 per QALY and the ICER was under £30,000 per QALY in 42% of PSA samples. In the adolescent cohort, the mean ICER was £26,175, and the ICER was under £30,000 per QALY for 72% of PSA samples. However, the ICER when using the weighted mean outcomes across both cohorts was £31,076 per QALY. It is not possible to estimate proportion of PSA samples that provide an ICER under £30,000 when using a weighted average approach as the model has to be run independently for each age group and the PSA samples are not correlated across runs.

Table 1: Results of the EAG's exploratory analyses for the whole cohort (≥ 12 years) and the age subgroups (12-18 years and ≥ 18 years) [a]

Option	QALYs	Costs	Incremental		ICER
			QALYs	Costs	
Unweighted by AT/AU prevalence or age [b]					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	£28,633
Subgroup aged 12-18 years subgroup					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	£25,892
Subgroup aged ≥ 18 years					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	£30,249
Whole population when using weighted outcomes average across the age categories and assuming 4.91% of patients with severe AA are aged 12-17 years					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	£29,986[c]
EAG threshold analysis - whole population when using weighted outcomes average across the age categories and assuming 4.65% of patients with severe AA are aged 12-17 years					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	£30,000

[a] *Deterministic ICERs*
[b] *This is for the whole cohort using average baseline characteristics and efficacy data pooled across the whole cohort and does not represent the committee's preference for weighting the average outcomes for young people and adults in the model separately*
[c] *Reported as £29,988 in Table 2 and Table 3 of the company's additional analyses*

Table 2: EAG base case and scenario results for subgroups with and without AT/AU [a]

Option	QALYs	Costs	Incremental		ICER
			QALYs	Costs	
AT/AU subgroup					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	£36,809
Non-AT/AU subgroup					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	£24,999
Whole cohort using weighted average approach across the AT/AU and non-AT/AU subgroups and the proportion with AT/AU estimated by the company (9.52%)					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted] [b]	£25,625 [c]

[a] Deterministic unless otherwise stated; does not use weighted average across age subgroups approach as this is not available for the AT/AU and non-AT/AU subgroups
[b] Reported as £[redacted] in Table 4 of the company's updated analyses which the EAG believes to be a typographical error
[c] Reported as £25,626 in Table 4 of the company's updated analyses which the EAG believes may be due to rounding differences in intermediate steps of the calculation

Table 3 Base case results when using the probabilistic sensitivity analysis [a]

Option	QALYs	Costs	Incremental		ICER
			QALYs	Costs	
TE-EA base case: Age 12-18 years subgroup					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	£26,175
TE-EA base case: Age ≥ 18 years subgroup					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	£31,399
TE-EA base case: Whole cohort (age ≥ 12 years) using weighted average across age subgroups					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	£31,076

[a] The EAG were unable to generate PSA results for the AT/AU and non-AT/AU subgroups.

5. Discussion

The EAG is satisfied that the company's updated analyses are consistent with the committee's preferences. It notes that there is some heterogeneity in cost-effectiveness within the eligible population, with treatment being more cost-effective in younger patients, largely due to the inclusion of a carer disutility for carers of young people, and treatment being more cost-effective in those without AT/AU, due to a lower proportion of those with AT/AU achieving a SALT score of ≤20 in the ALLEGRO trial. Therefore, the cost-effectiveness across the population covered by the company's anticipated marketing authorisation, is dependent on the characteristics of those likely to receive treatment in current practice. The EAG notes that the average ICER may be above £30,000 per QALY if young people make up a smaller proportion of the treated population than estimated by the company, and that the EAG have some concerns regarding the methods used to estimate this proportion. In addition, the average ICER based on the PSA was over £30,000 per QALY when using weighted outcomes across age groups. However, the analyses using weighted outcomes across age groups do not adjust for the fact that patients with AT/AU were oversampled in the trial population which would bias the ICER upwards. Therefore the EAG considers that there remains some uncertainty regarding the most plausible ICER, but it is likely to be in the range of £25,625 to £31,076 per QALY.

References

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Ritlecitinib for treating severe alopecia areata in people 12 years and over. A Single Technology Appraisal

Third addendum: Critique of the company's response to the Draft Guidance Document

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1. Introduction

In November 2023, NICE published draft guidance for consultation on ritlecitinib for treating severe alopecia areata (AA) in people aged 12 years and over.[1] The company has provided a response to the draft guidance document (DGD) including additional evidence and NICE has asked the EAG to provide a critique of this additional evidence.[2] The company's DGD response included a set of analyses for a scenario which the company describes as capturing the committee's preferred assumptions and which provided ICERs ranging from £25,626-£29,988 per QALY.[2] These analyses had been submitted to NICE by the company in October 2023[3] in response to a request by NICE and the EAG has previously critiqued these analyses in their second addendum to the EAG report dated 20th October 2023. As such no further critique will be provided here on these scenarios, but these scenarios are briefly described in Section 3.1 for reference. In this third addendum to the EAG report, the EAG has focused on assessing new evidence provided by the company in response to consultation which has not been previously critiqued by the EAG. This third addendum should be read in conjunction with the EAG report and the previous addenda.

All results presented in this document include the revised PAS discount which reduces the cost per pack of 30 capsules from a list price of £[redacted] to £[redacted], equivalent to a simple discount of [redacted]% on the list price.[2]

2. Summary of the additional evidence submitted in the company's response to the DGD

The company has provided the following additional evidence:

- Long-term follow-up data from ALLEGRO LT for the EQ-5D (also provided in their October 2023 response but not previously critiqued by the EAG)
- EQ-5D scores from ALLEGRO 2b/3 and ALLEGRO LT stratified by SALT score to align with the definition of the heath states in the economic analysis
- An assessment of the psychometric performance of the EQ-5D and SF-36 using data from the ALLEGRO trial
- A review of studies in AA reporting EQ-5D, SF-36 and DLQI
- A new vignette study in which the vignettes previously valued using time-trade-off (TTO) in a general population sample were valued using TTO in a cohort of patients with AA
- A multicomponent scoping review to describe utility values for atopic dermatitis and their suitability for use as a proxy condition for utilities in AA
- Cost-effectiveness analyses incorporating alternative utility values including:

    - TTO valuations of the vignettes using a sample of patients with AA
    - utility values from the literature in patients with atopic dermatitis
    - utility values from the full-text publication (Vañó-Galván et al)[4] describing the European cohort from the Adelphi Database, previously described only in abstract form by Bewley *et al.*[5]
- Cost-effectiveness analyses exploring the impact of including pharmacological treatment within best supportive care (BSC)
- Cost-effectiveness analyses exploring different approaches to estimate time on treatment

The EAG has divided its critique into three topic areas as follows:

1) Does the evidence demonstrate that the EQ-5D is not an appropriate measure of health utility in people with AA? (section 2.1)
2) Are any of the alternative utility values provided by the company more appropriate and are the estimates provided robust? (section 2.2)
3) Are any of the company's additional cost-effectiveness scenario analyses plausible alternatives to the committee's preferred DGD base case? (section 3)

2.1 Is the EQ-5D an appropriate measure of health utility in people with AA?

2.1.1. Long-term EQ-5D data from ALLEGRO LT

The company presents long-term EQ-5D from ALLEGRO LT (Figures 1 and 3 of the DGD response)[2] and argues that these demonstrate that the EQ-5D is not an appropriate measure in AA because they show that the health utility in the study population is high at baseline and continues to remain high. It argues that there is a ceiling effect, whereby a high proportion of patients who have severe AA report full health utility making it difficult to demonstrate an improvement in EQ-5D. The company also presents average EQ-5D scores over time by SALT score (Figures 2 and 4 of the DGD response)[2], stating that these shows low variability in EQ-5D for patients with different SALT scores. The company argues that the consistent high scores over 24 months suggest that the lack of improvement in the EQ-5D is not due to the limited duration of follow-up as previously suggested by the EAG.

The EAG considers that the psychometric analysis of the ALLEGRO data discussed in section 2.1.2 provides a much better assessment of whether there are issues with ceiling effects in the ALLEGRO study than the plots provided in Figures 1 to 4 of the company's DGD response.[2] The EAG notes that there is substantial loss to follow-up, with more than [redacted]% of the modified *de novo* cohort and more than [redacted]% of the roll-over 50mg cohort being loss to follow-up at 24 months in ALLEGRO LT. It is therefore difficult to assess whether EQ-5D is stable over time.

The EAG is concerned that the information from the company on the time periods reported in Figures 1 and 2 is somewhat contradictory making it unclear whether the longest duration of follow-up for EQ-5D outcomes is 24 months or 36 months from the start of treatment in those patients rolling over from ALLEGRO 2b/3. The EAG is also unclear how the cohorts presented in Figures 1 to 4 have been selected and how they relate to cohorts previously presented in the company's response to technical engagement. However, as these are minor issues, which may be resolved with further explanation from the company, the EAG's discussion of these points is provided in Appendix 1.

The EAG notes that the committee stated that, "*it would like to see cost-effectiveness estimates which included all its preferred assumptions as well as a scenario using the EQ-5D data from ALLEGRO-LT.*"[1] The company has provided utility weights for adult patients from the ALLEGRO 2b/3 study at 48 weeks and from the ALLEGRO-LT at 24 months (Table 13 and Table 14 in Appendix B of the company's DGD response).[2] These were obtained using a mixed effects model for repeated measures, adjusted for age and baseline utility. The EAG noted that minimal information was provided by the company on the number of patients or observations incorporated in these analyses or the methods of these analyses. The EAG is therefore unable to provide a substantive critique of these analyses. The company has not incorporated these utility values into the economic model due to their concerns regarding the suitability of the EQ-5D as a measure of health utility in AA. [2]

The EAG remains concerned that the exclusion of patients with psychiatric comorbidities from the trials and the long average duration of since diagnosis at baseline may have resulted in a trial population which was less likely to report severe problems on the EQ-5D questionnaire. For this reason, the EAG still prefers to use the estimates from the European cohort of the Adelphi database cross-sectional study reported in the literature to inform the EQ-5D scores by health state (further discussed in Section 2.2.1). However, the EAG has also presented scenario analyses in which the utility values from the ALLEGRO LT study are incorporated into the economic model (see Sections 3.2 and 4.4).

2.1.2 Psychometric analysis of data from ALLEGRO

The company has provided an assessment of the psychometric performance of the EQ-5D and SF-36 using data from the ALLEGRO 2b/3 trial (company's DGD response p15-16 & full report by Law and LLoyd).[2, 6] This analysis is more detailed than the previous analysis of the ALLEGRO trial data by Lloyd *et al.* which was provided by the company at technical engagement.[7] The company concludes that this analysis demonstrates that both EQ-5D and SF-36 have limited ability to assess the full HRQoL impacts associated with AA experienced by patients over time.

The psychometric analysis is based on baseline, week 24 and week 48 data from the ALLEGRO-2b/3 clinical trial (N=[redacted]; n=[redacted] adolescents; n=[redacted] adults).[6] The authors acknowledge that this is not an ideal dataset in which to assess the performance of EQ-5D given that all patients had SALT scores ≥50 at baseline, and the adolescent sub-samples were too small to perform known group analysis for the EQ-5D-Y.

The EQ-5D displays ceiling effects in this data, with over [redacted] of participants ([redacted]%) reporting the highest EQ-5D score (e.g. 11111). Histograms are used to demonstrate that patients reporting full health (11111) on the EQ-5D [redacted] The mean duration of AA since first diagnosis for the sample is 10.1 years and it is unclear if this ceiling effect would be found with more recently diagnosed patients.

Known group validity analysis compared scores for patients moving to a SALT score <10 at weeks 24 and 48. [redacted] effect sizes were identified for the EQ-5D-5L at week 48 ([redacted]), but not EQ-5D-Y. The AAPPO sub-scores both showed [redacted]; Emotional symptoms ([redacted]), Activity limitations subscale ([redacted]) (Psychometric report, Appendix E). This pattern is replicated when using the PGI-C (Patient Global Impression of Change) as a measure of response, with EQ-5D-5L identifying [redacted] effect sizes, and the AAPPO sub-scores showing [redacted] effect sizes than either the [redacted].

Sub-groups of patients were also defined by high (scores of >2) and low (scores of <=2) on the AAPPO subscales. These groups had quite [redacted] on the EQ-5D-5L and SF-36 PCS and MCS subscale scores at most time points, and [redacted] in the EQ-5D-Y for the AAPPO Emotional symptoms subscore. For example, at baseline mean EQ-5D-5L scores for those with an Emotional symptoms subscore <=2 (n=[redacted]) was [redacted] (SD [redacted]) and for those with an Emotional symptoms subscore >2 (n=[redacted]) the mean EQ-5D score was [redacted] (SD [redacted]) (d=[redacted]) (Appendix G and H).

All outcome measures are [redacted] correlated with the SALT score. Across all time periods the correlation is [redacted] for the AAPPO sub-scales ([redacted] Emotional symptoms; [redacted] for Activity limitation) than EQ-5D-5L ([redacted]), SF-36 MCS [redacted]), SF-36 PCS [redacted]), and EQ-5D-Y [redacted] These [redacted] correlations may reflect the lack of a linear relationship between HRQoL and percentage of hair loss which has been identified in other work (Gelhorn et al, 2022; Shi et al, 2013).[8, 9]

An exploratory factor analysis was conducted which identified nine factors. [redacted] Authors suggest this implies that the AAPPO may capture distinct aspects of HRQoL in patients, however, this may also be driven by the different wording and response options used in the AAPPO generating a methods effect. Some items within the AAPPO conceptually overlap with other factors. For example, AAPPO item 10 (physical activities) is similar to items contained in factor number nine which contains physical functioning items from the other instruments, similarly, the AAPPO item 7 (sad) is similar conceptually to other items in factor number one which contains the emotional wellbeing items from the SF-36.

The EAG notes that the psychometric report also concludes that, *"The psychometric properties of other generic instruments, such as the SF-6D, could also be used to assess HRQL in this population and further explore the properties of the EQ-5D and SF-36."*[6] The EAG is unclear why the authors described an assessment of convergent validity using the SF-6D as a research aim (pg11)[6] but fail to present any analysis using SF-6D. The EAG notes that the SF-36 MCS appears to perform similarly to the EQ-5D and therefore an exploration of utility values based on SF-6D would be useful.

Overall, the EAG considered that the psychometric performance of the EQ-5D-5L from this analysis is mixed. The EQ-5D-5L shows known group validity between high and low AAPPO subscale scores but has relatively poor responsiveness compared to the AAPPO and displays high ceiling effects in this dataset. The greater sensitivity and responsiveness of the condition specific measure would be expected when comparing to a generic instrument. The psychometric performance of the EQ-5D-Y is weaker but, as noted by the authors, the data is not ideal for assessing the performance of the EQ-5D-Y. The three level EQ-5D-Y may lack sensitivity for adolescents with AA. The psychosocial domains of embarrassment, self-consciousness, and fear of being bullied were identified in a recent review of eight studies as the quality of life domains most consistently affected by AA in under 18s.[10] The EQ-5D-Y may therefore underestimate HRQoL impacts of AA for the 12-17 year old patients.

2.2 Has the company provided any new utility estimates that are more appropriate than those previously considered by the committee?

2.2.1 Updated review of generic and condition specific quality-of-life measures in AA

The company has provided a review of the quality-of-life literature (Appendix A of the company's DGD response)[2] focusing on studies reporting HRQoL measured by EQ-5D, SF-36 or DLQI. The EAG does not consider this to be new evidence as it appears to be repetition of a review conducted to inform the vignette study.[11] No information is provided on the date of the last searches, although the full report

of the review is dated April 2022 and the EAG notes that no studies have been included that were published after 2021. The EAG note in particular that the review does not identify either the recently published full-text paper by Vañó-Galván *et al.*[4] or the paper by Edson-Heredia *et al.*,[12] which was published in 2022. Given these uncertainties, the EAG cannot be sure that no recent relevant studies were missing from the company's review.

Whilst this review does not appear to be new evidence, this review is useful in assessing whether there are any estimates from other generic or condition specific measures that could be used as an alternative to the EQ-5D in this population and whether these are likely to be more appropriate than estimates based on the EQ-5D. The company conclude that there are no preference-based condition specific measures in AA, as the AAPPO is not preference-based.[2] The systematic review (DGG response, Appendix A)[2] concludes that the DLQI (a HRQoL measure designed for dermatological conditions) is potentially more sensitive in AA. As there is no set of preference-based scores for the DLQI, the company discusses whether mapping is possible from the DLQI to the EQ-5D using mapping algorithms developed in other skin conditions, such as psoriasis. However, they conclude that this is not appropriate given the concerns raised about the applicability of the DLQI in patients with AA and the company's concerns regarding the applicability of the EQ-5D.[2] It also notes the lack of DLQI measurement in the ALLEGRO clinical trials, meaning that any estimate of utility would need to come from DLQI scores reported in the literature. The EAG is broadly satisfied that obtaining utilities from the DLQI is unlikely to be feasible with the current evidence available.

The company identified three papers reporting AQoL-8D in patients with AA,[13-15] which have been previously described by the EAG (EAG report pg 106). Two of these papers describes outcomes from an RCT of cyclosporine versus placebo,[14, 15] with one of these reporting a secondary analysis exploring the impact of AA on HRQoL.[15] The secondary analysis of HRQoL outcomes suggests that AQoL-8D has reasonable psychometric performance in AA. The authors also note that the AQoL-8D was selected as an outcome in this RCT because it more comprehensively evaluates psychosocial dimensions than the EQ-5D.[15] However, this paper only provides utility scores for alopecia totalis/alopecia universalis (AT/AU) and 'patchy AA,' and therefore it could not be used to populate the model without the company requesting further analysis of the data by SALT score from the authors. The third paper reporting AQoL-8D is a roll-over study in which non-responders from the cyclosporine RCT were offered tofacitinib.[13] The EAG notes that the company's incorrectly quotes the observed utility change in this study as follows: "*a mean SALT score reduction of 15.57 (%) from baseline over 12 weeks which was associated with an AQoL-8D utility improvement (0.515) over this period.*"[2] Whereas in fact the utility improvement based on AQoL-8D was 0.0148 with a p-value of 0.0515. However, this study also does not provide utility scores by SALT category.[13] The EAG concludes from these studies that whilst

the AQoL-8D instrument is a promising generic measure of HRQoL in AA, the company's review has not identified any AQoL-8D based estimates in the literature that can be used directly in the model.

The review also identified two studies describing the use of the SF-36 in patients with AA that provided scores for patients with different degrees of hair loss.[16, 17] Masmoudi *et al.* reported statistically significant differences in two SF-36 domains (mental health and social functioning) by extensiveness of hair loss, but no statistically significant difference when using the mean score across all domains.[16] Ghajarzadeh *et al.* reported no significant differences by % scalp involvement, [17] although the study only reports a comparison of the average SF-36 score across all domains and therefore it may have failed to have detected differences in individual domains which were identified by Masmoudi *et al.* The EAG notes that for Masmoudi *et al.*,[16] the company reports that, "*Utility values have previously been estimated with these data at Pfizer using a mapping algorithm for an early economic model,"*[2] but the company does not provide these utility estimates. The EAG would have preferred the company to have presented these utility estimates as they may have provided an alternative to the EQ-5D estimates from the literature. The EAG also notes that the company could equally have estimated utility values from the SF-36 outcomes collected in the ALLEGRO trial using the SF-6D valuation set. Although the EAG acknowledges that these would also be subject to the concerns previously raised regarding the trial population (i.e. long average duration since diagnosis and exclusion of patients with psychiatric comorbidity).

As the review also includes studies reporting the EQ-5D it is possible that it could provide evidence on the psychometric performance of the EQ-5D to supplement that provided by the ALLEGRO trial. The review reports having identified only 2 studies reporting EQ-5D in patients with AA, and only one of these reports EQ-5D by physician reported severity, which is the abstract by Burge *et al.* reporting results from the Adelphi Database for a US cohort.[18] However, it is also important to consider the literature known to be missing from the company's review, the most relevant of which is the cross-sectional study using the European cohort of the Adelphi Database, previously identified by the EAG as being reported in an abstract by Bewley *et al.*[5] This abstract reports data from the same Adelphi Database, but for a European cohort,[5] and is therefore more relevant than the US cohort reported by Burge *et al.*[18] The full text from this study is now available in a publication by Vañó-Galván *et al.* and this provides EQ-5D values according to physician assessed severity states of mild, moderate and severe AA.[4] The utility estimates from the full-text manuscript are very close to those provided in the abstract (data presented later in Section 3.2, Table 2). Vañó-Galván *et al.* state that the anxiety/depression domain and the pain/discomfort domain of the EQ-5D were most affected by AA, with minimal impact on the other domains.[4] However, the EAG note that the usual activity domain was also statistically significantly associated with physician rated AA severity, albeit with a higher proportion reporting 'no problems' on the usual activity domain than for either the anxiety/depression or pain/discomfort

domains. The EAG also notes that whilst the proportion of patients with severe AA self-reporting anxiety or depression as a comorbidity was low in this cohort (6.4% for both), the proportion scoring over ≥11 on the HADs scale was 29% for anxiety and 27% for depression. Therefore, the EAG considers that the data from this cohort is more representative than the data from the ALLEGRO trial which excluded patients with depression and suicidal ideation. The EAG accepts that the Adelphi database study used physician rated severity to class patients as having either mild, moderate or severe AA and therefore it is possible that these classifications may not align exactly with the health states in the model. However, there was substantial agreement between physician and patient reported severity and the company previously stated that, "*the majority of clinicians in the UK use the SALT score to define severity of AA*," (CS, pg20)[19] suggesting that a reasonable correlation would be expected between SALT scores and physician assessed severity. Furthermore, Vañó-Galván *et al.* report mean (SD) % of scalp hair loss due to AA as follows: 9.2% (SD 6.2%) for mild AA, 31.3% (SD 10.4%) for moderate AA and 71.4% (SD 19.5%) for severe AA.[4] This suggests that there would be reasonable correlation between the physician rated severity categories and the health states defined by SALT scores to which the EAG has applied these utility estimates (i.e. scalp hair loss of ≤20% for mild, 21% to 49% for moderate and ≥50% for severe AA). Although this study included patients from the UK, and used the UK EQ-5D valuation set, the authors report that the majority of the participants were from Germany (61%) or Spain (27%). The EAG considers this a minor issue in terms of generalisability, especially when considering that similar findings were reported across Japanese and US samples,[12, 18] albeit with higher absolute utility values in the US sample. Overall, the EAG is satisfied that the full-text publication by Vañó-Galván *et al.* further supports their previous conclusion that the data from this cross-sectional study, using the European cohort of the Adelphi database, can be applied in the cost-effectiveness model as an alternative to the EQ-5D data from the ALLEGRO trial. Application of these estimates in the cost-effectiveness analysis is further explored in Section 3.2.

2.2.2 Vignette study using patients with AA instead of a general population sample

The company has provided a new vignette study in which the vignettes previously valued using TTO in a general population sample were valued using TTO in a cohort of patients with AA. This is described on pages 18 to 22 of the company's response to the DGD and in more detail in a full study report.[2, 20] The aim of this study was to address the concern that the public may have over-estimated the impact of the health states on utility because they underestimate the ability of patients to adapt and cope with their condition. Therefore, the original TTO valuation was replicated using patients with AA instead of members of the general public to conduct the TTO valuations. The company states that the results show consistency between the TTO valuations provided by the patients and the general public. The company has included a scenario analysis in which they apply the utility values from the valuation of the vignettes by patients in the economic model. This analysis and the utility values applied can be found in Section 3.2.

The EAG notes that best practice would be to use members of the general population to value the health states, (see hierarchy of evidence from NICE methods guide[21], reproduced in Figure 5 of the company's DGD response[2]) as was done in the original study.[22] Therefore, the new study using patients to value the vignette health states does not really provide any evidence which is more robust than that provided in the original vignette study. In addition, the company has used the same vignettes descriptions despite the EAG previously raising concerns about the face validity of these vignette descriptions (see EAG report pg 129-130 & first addendum pg 24-25). The company reports 'qualitative observations' from the new vignette study, but the EAG notes that the vignette study did not include a formal qualitative component. These qualitative observations appear to be based on summarising *"field notes"* collected by the moderators, *"to give additional context to understand participant's valuations or task comprehension."*[20] The EAG therefore considers that the company's conclusions based on these 'qualitative observations' should be interpreted with caution as a formal qualitative study of the validity of the vignettes as perceived by the patients included in the TTO exercise was not conducted. In addition, having re-examined the original and the newly submitted vignette studies,[20, 22] the EAG has identified an additional concern regarding the research methodology. Both TTO studies employ a video conference method in which "*the interviewer presented the TTO board and the VAS to the participant by holding these up next to themselves on the screen*" (Aggio, Nov 2022, pp19).[22] It is not known whether this would have the same validity as a face to face interview and any evidence suggesting equivalence of face to face compared with video conferencing TTO data collection when using a computer assisted personal interviewing (CAPI) system (e.g. Rowen et al, 2022)[23] can not be used as validity evidence. Despite these concerns, for completeness the EAG has provided a scenario analysis using the committee's preferred DGD assumptions combined with the new utility values obtained using patients to value the vignettes in Section 3.2.

2.2.3. Proxy utility values from atopic dermatitis

The company has provided a multicomponent scoping review to describe utility values for atopic dermatitis which the company argues can be used as a proxy condition to estimate utilities for AA. The EAG notes that according to the hierarchy of evidence[21] (reproduced by the company in Figure 5 of the company's DGD response[2]), using EQ-5D utility values from a proxy condition is further down the hierarchy than using EQ-5D utility values from the literature for the condition of interest. For this reason, and given the limited time the EAG had to review the company's response to the DGD, the EAG has not spent time critiquing the company's review of utility values in atopic dermatitis. However, as the company provided a scenario using estimates from AA combined with the company's base case preferences, for completeness the EAG has provided a similar scenario analysis using the committee's preferred DGD based case as its starting point (see Section 3.2).

3. Company and EAG's additional cost-effectiveness analyses

3.1 Recap of the company base case scenario and the committee preferred scenario in the DGD

The company has provided some additional cost-effectiveness analyses in its response to the DGD.[2] The company has not updated its preferred base case since technical engagement (other than to include its updated PAS described in Section 1). However, it has also provided a scenario described as the committee preferred base-case, which the EAG has previously confirmed is aligned with the EAG's base case following technical engagement (see EAG report addendum 2). The key differences between these two scenarios are:

- the EAG uses the average transition matrix from the second year to estimate transitions beyond 2 years whereas the company assumes a steady state;
- the EAG applied the published utility data from the European cohort of the Adelphi Database (Bewley *et al.*)[5] whereas the company applied data from the vignette study with valuations by the general public;
- the EAG selected the exponential distribution to extrapolate time to discontinuation in response to treatment, whereas the company preferred the Weibull distribution;

For a more detailed discussion of these differences see EAG report addendum 1, Table 2.

The company's base case provides an ICER of £8,294 across the whole population (aged 12 years and over) when using average baseline characteristics. However, the ICERs were £7,986 for adolescents (aged 12 to 17 years) and £8,940 for adults. The company does not provide an ICER calculated as the average across age subgroups for the company's base case. However, the EAG estimates that it would be £8,026 based on the company's estimate that 4.91% of patients with severe AA are adolescents (see Appendix 2, Table 8). Results for the company base case for subgroups with and without AT/AU and were not provided by the company. However, as the committee concluded that it preferred to consider an ICER weighted by alopecia severity (DGD Section 3.16), results for these subgroups have been extracted from the model by the EAG and a weighted average has also been calculated (see Appendix 2, Table 8).

The company's scenario based on the committee's preferences in the DGD provides an ICER of £28,633 across the whole population (aged 12 years and over) when using average baseline characteristics. However, the ICERs were £25,892 for adolescents (aged 12 to 17 years) and £30,249 for adults. When using a weighted average and assuming 4.91% of the population are adolescents, the ICER was £29,986. The company also provided an average ICER when weighting across subgroups defined according to whether patients had AT/AU or did not have AT/AU for this committee preferred scenario. The ICER across the whole population when assuming that 9.52% of patients had AT/AU was

£25,625 for the committee's preferred DGD base case. Full results for these scenarios have been previously reported in EAG report addendum 2.

In their response to the DGD, the company has provided some additional cost-effectiveness analyses exploring the application of alternative utility values (see Section 3.2), the inclusion of BSC costs (Section 3.3) and additional scenarios of treatment waning (see Section 3.4).[2] The results are reported for the whole population (aged 12 years and over) using average baseline characteristics. They therefore do not reflect the committee's preferred approach of using a weighted average ICER across either age categories (i.e. adolescents aged 12 to 17 years and people aged 18 years and over) or subgroups with or without AT/AU. However, this approach of presenting an ICER for the whole population allows the impact of each change to the base case scenario to be presented using a single figure. Therefore, the EAG has also used this approach in Section 3 when presenting information on the impact of each change to the base case, but the EAG has also provided full results using the weighted average approach for a narrower range of scenarios in Section 4.

3.2 Application of alternative utility values

The company has provided several scenario analyses exploring the impact on the ICER of using utility values from different sources, with some of these being conducted using the company's base case as the starting point and some being conducted using the committee's preferred assumptions at DGD as the starting point. The EAG has therefore provided ICERs when incorporating each set of utility values into either the company's base case or the committee preferred scenario in the DGD (Table 1). The ICERs in italics in Table 1 are those already provided in the company's DGD response, with all other ICERs being those obtained by the EAG.

The EAG was able to validate the company's ICER for the application of the data from Vañó-Galván *et al.*, [4] (full-text paper for Bewely et al. abstract[5]). The utility values were close to those previously reported in the abstract, but with slightly higher sample sizes reported (N=184 for severe; N=275 for moderate and N=97 for mild). The EAG prefers the updated estimates provided by Vañó-Galván *et al.*,[4] over those reported by Bewley *et al.*, (see Section 2.2.1) but notes that the ICERs are very consistent across these two sources.

The company also explored using the data from the new vignette study (see Section 2.2.2) in which the health states were valued by patients with AA rather than by the general public.[20]. However, there was a small discrepancy between the ICER obtained by the EAG and that reported by the company for this scenario (see Table 1). The EAG believe this is because the company inputted the data rounded to 2 decimal places (d.p.) rather than the values rounded to 3 d.p provided in their report and they also did not update the utility values used to derive the carer disutility. However, as the company's revised

model did not incorporate any of their updated utility analyses and the EAG was obliged to replicate them manually, the EAG cannot be exactly sure of the reason for the discrepancy. However, this discrepancy was small and did not change the general conclusion that the ICERs are much lower when using the utility values from the vignette study than when using the utility values obtained from the European cohort of the Adelphi database (Bewley *et al.*, and Vañó-Galván *et al.*).[4, 5]

The company also provided an ICER for a scenario in which they included utility values from patients with atopic dermatitis as a proxy condition. These are described as using the 'central estimates' from those identified in the literature for mild, moderate and severe atopic dermatitis.[2] The EAG identified through trial and error that these were the midpoint between the upper and lower values provided for 'all studies' in Table 5 (pg26) of the company's DGD response.[2] Whilst the EAG was able to validate the company's ICER for this scenario and provide a similar analysis using the committee's preferred base case, the EAG considers that these estimates are less relevant than the EQ-5D estimates obtained from the literature (see Section 2.2.3).

The EAG also conducted scenario analyses in which it inputted the utility values obtained by the company using linear mixed modelling on the 48 week data from Allegro 2b/3 and the 24 month data from ALLEGRO LT (see Section 2.1.1). These scenarios provided a much small difference in utility between patients with severe and mild AA (see Table 1). As such, they resulted in much higher ICERs which were above £100,000 per QALY when using either the company' base case or the committee's preferred assumptions.

Overall, these scenario analyses demonstrate that the ICER is extremely sensitive to the utility values incorporated in the analysis. Given the concerns regarding the exclusion of patients with mental health comorbidities from the ALLEGRO trials, and the high baseline EQ-5D scores which may reflect the recruitment of patients with a high degree of adaptation (DGD Section 3.13), the EAG prefers to include the utility values from Vañó-Galván *et al.*,[4] in their base case analysis (see Section 4.1). However, the EAG has included full results for the scenario analysis using the utility values from the ALLEGRO trial as this scenario was requested by the committee in the DGD (see Section 4.4) and this approach is consistent with the NICE reference case.[21]

Table 1 Alternative utility values applied in the model and the impact on the ICER (full population aged >12 using average baseline characteristics i.e. not weighted by age or AU/AT severity)

Health state	Vignettes valued by general population[22]	Vignettes valued by patients with AA[20]	Bewley *et al.* (abstract)[5]	Vañó-Galván *et al.*[4]	Allegro 2b/3 trial data at 48 weeks[2]	Allegro LT data at 24 months[2]	Atopic dermatitis (literature)[2]
Patient with SALT 50-100	[redacted]	[redacted]	0.78	0.77	[redacted]	[redacted]	0.67
Patient with SALT 21-49	[redacted]	[redacted]	0.85	0.85	[redacted]	[redacted]	0.78
Patient with SALT 11-20	[redacted]	[redacted]	0.90	0.89	[redacted]	[redacted]	0.83
Patient with SALT 0-10	[redacted]	[redacted]	0.90	0.89	[redacted]	[redacted]	0.83
Caregiver to adolescent with SALT 50-100	[redacted]	[redacted]	NR [a]	NR [a]	NR [a]	NR [a]	NR [a]
ICER when combined with company's base case	*£8,294*	£*7,767* (company) [b] £7,606 (EAG) [c]	*£23,914*	£23,815	£109,330	£129,673	*£17,973*
ICER when combined with committee's DGD preferences	£10,192	£9,320	*£28,633*	*£28,367*	£120,970	£142,860	£21,542

[a] *Caregiver disutilities not reported in these sources so in these scenarios caregiver disutilities were estimated using the caregiver utility values from the vignettes valued by the general population.*

[b] *This ICER can be obtained by inputting the patient TTO utility values rounded to 2 d.p and assuming that the caregiver disutility is still based on TTO completed by a general population sample.*

[c] *The EAG's approach uses the utility values rounded to 3 d.p and applies the caregiver disutility from the AA patient sample – an ICER of £7,682 is obtained if the caregiver disutility is based on the general population TTO sample.*

3.3 Inclusion of BSC costs

The company has provided a scenario analysis in which it includes a 'basket' of pharmacological treatments for patients having BSC (company response to DGD, Table 7).[2] The EAG disagrees that this is a relevant scenario analysis given that the company has previously argued that the appropriate comparator for ritlecitinib is non-pharmacological management (CS, Section B.1.3.3.6 & B.3.2.2).[19] If BSC is to be defined as including a 'basket' of pharmacological treatments, then the model should reflect the effectiveness of these treatments. The company's scenario analysis incorporates costs for this 'basket' of pharmacological treatments but does not include any potential for these treatments to be effective. In addition, the company has previously stated that, *"the vast majority of patients with severe AA are not receiving any pharmacological treatment,"* (CS, B.1.3.3.2)[19] whereas their scenario analysis assumes that only 12%-13% of patients do not receive pharmacological treatment as part of BSC (Company response to DGD, Table 5, pg31).[2] If such a high proportion of patients are receiving pharmacological treatments at part of BSC, then using the placebo arm of the ALLEGRO 2b/3 trial to estimate expected costs and benefits in the absence of ritlecitinib is inappropriate and a full incremental analysis is required considering both the costs and benefits of pharmacological alternatives to ritlecitinib.

The company has used the estimates of resource use for pharmacological BSC from TA926 in its scenario analyses, but has not provided any description of the two data sources used in TA926 (Adelphi Disease Specific Programme [DSP] and Key Opinion Leader [KOL]).[2] From examining the committee papers for TA926, the EAG believes that these data are based on 117 UK patients with severe/very severe AA. The EAG has had limited opportunity to assess whether the costs included for pharmacological BSC in the company's scenario analyses are consistent with those used in TA926 and whether they reasonable. However, it notes that only drug acquisition costs are included, which may underestimate BSC costs for interventions requiring secondary care administration (e.g. contact immunotherapy) or intensive monitoring that is more frequent than that assumed for patients having non-pharmacological BSC. The EAG also notes the comment from the British Association of Dermatologists (BAD) that there are data available from the ADAAGIO study on pharmacological treatments for UK patients with severe AA (N=[redacted]) based on responses from UK dermatologists (n=[redacted]).[24] The figures provided by BAD in its DGD response suggest higher use of systemic corticosteroids ([redacted]% versus 17% to 25%) and lower use of systemic immunosuppressants ([redacted]% versus 29% to 32%) compared with the data from the Adelphi DSP and KOL sources (company response to DGD, pg31, Table 5)[2] used by the company in their response to the DGD. The EAG is unclear why these data have not been provided by the company given that the BAD submission indicates that the ADAAGIO study was conducted by Pfizer. The EAG therefore considers that there is significant uncertainty regarding the appropriate mix of pharmacological treatments and as such believes that the scenario analysis provided by the company should be viewed with caution.

Furthermore, the scenario analysis including pharmacological treatments within BSC assumes that patients may continue to use these treatments for up to 10 years. The EAG considers this duration of treatment to be unlikely if the treatments are not expected to have any clinical effectiveness, such that all patients receiving pharmacological BSC in the model are assumed to continue to have a SALT score ≥50. The EAG notes that in the baricitinib appraisal, the duration of pharmacological BSC was restricted to 10-years after clinical experts noted that there were, "*multiple treatments available for alopecia areata, for which each treatment would normally be tried for 6 to 12 months.*"[25] The company describes maximum treatment durations for pharmacological BSC in Table 5 of the DGD response as follows: 1 year for azathioprine and mycophenolate mofetil; 9 months for contact immunotherapy; 23 weeks for anthralin cream and 16 weeks for Minoxidil 5% foam.[2] In addition, the EAG notes that in the document describing the company's elicitation of expert opinion to understand the UK therapeutic landscape, concerns were raised regarding the long-term use of ciclosporin given concerns around renal impairment.[26] This document also describes oral steroids as being limited to 3 to 6 months, but there is no restriction on duration of prednisolone in the model.[26] For those treatments where a maximum treatment duration is specified, the company calculates the cost per annum using these maximum durations and then applies the same cost every year for 10 years. This means, for example, that the 21.63% of patients who receive contact immunotherapy are assumed to receive it for 9 months of the year every year for 10 years. The company's implementation may be appropriate if the interpretation of the Adelphi DSP data is that at any one time these proportions of patients having BSC will be receiving these treatments, rather than these being the proportions of patients starting each treatment when failing to achieve a response on either ritlecitinib or non-pharmacological BSC. However, this interpretation of the data would suggest that 21.63% of patients with severe AA will be having contact immunotherapy at any one time, meaning that all patients with severe AA will have completed one 9-month contact immunotherapy course within 5 years. These estimates seem inconsistent with the company's statement that contact immunotherapy is not widely available in the UK (CS, pg44).[19] Overall, the EAG is not convinced that assuming a 10-year treatment duration for pharmacological treatments is reasonable when they are assumed in the model to have no clinical effectiveness and many of the treatments can only be given for a limited duration. It has therefore provided as scenario in which the maximum duration of treatment for pharmacological BSC treatments is 2 years (see Table 2).

The company has explored scenarios in which the difference in BSC costs for ritlecitinib ranges from 0% to 75%, but these were only provided using the company's base case as the starting point (company response to DGD, Table 7).[2] Therefore, for completeness, the EAG has provided a similar set of scenario analyses using the committee's preferred base case scenario as the starting point (see Table 2). In TA926 the committee considered that both arms ('no active treatment' and baricitinib) should have the same proportions receiving BSC, but only a proportion of patients would receive BSC in both arms.[25]

Therefore, the committee's conclusion in TA926 suggests that the scenario analysis examining a 0% difference between the baricitinib and BSC arms was previously considered most plausible in TA926.[25] This would correspond to the 0% difference scenarios presented in Table 2, with ICERs ranging from £23,213 to £27,726, depending on the source of resource use data (KOL or Adelphi DSP) and the assumed duration of pharmacological BSC (10 years or 2 years).

The EAG notes that the company's scenarios that assume a difference in BSC between the two arms essentially assume that patients who have stopped ritlecitinib treatment and who are assumed to return to having severe AA (SALT >50), will use less pharmacological treatments in future that those who have severe AA after not having tried ritlecitinib. This leads to ritlecitinib dominating BSC in some of the scenarios presented in Table 2. For example, in the scenario in which the resource use is based on Adelphi DSP, and the reduction in pharmacological BSC usage in the ritlecitinib arm is 75%, ritlecitinib dominates BSC because the lifetime discounted BSC costs are £[redacted] in the BSC arm and £[redacted] in the ritlecitinib arm, providing a substantial cost saving of £[redacted], which more than offsets the lifetime drug acquisition costs for ritlecitinib of £[redacted] (figures extracted from model by EAG). The cost saving in this scenario is based purely on an assumption that pharmacological usage will be lower if ritlecitinib is offered even in those patients who have stopped ritlecitinib treatment and returned to their pre-treatment health state of severe AA. The company does not explore any scenarios in which patients are encouraged by a successful period of treatment with ritlecitinib and are therefore more likely to seek out further pharmacological treatment with another agent or indeed a second course of ritlecitinib treatment. In the absence of any empirical evidence on pharmacological resource use after ritlecitinib treatment, the EAG would argue that the likelihood of patients wanting further treatments should be based purely on whether they are currently experiencing severe AA and not on their treatment history.

Whilst the committee in TA926 stated that the analyses that applied the maximum BSC use in both arms reflected the committee's preferred assumptions,[25] information on the proportion of patients receiving BSC in the various scenarios considered by the committee is redacted from the committee papers for TA926. The only non-redacted figure was a scenario which assumed that 30% of patients in the 'no active treatment' arm receive pharmacological BSC.[27] The EAG notes that Table 5 (pg31) of the company's DGD response shows 12% having no active treatment according to the Adelphi DSP, suggesting that 88% are receiving active treatment.[2] The EAG has conducted a scenario analysis in which it reduces the proportion having pharmacological BSC down to 30% by applying a reduction factor of 0.34 (=30/88) to the costs. It should be noted that due to the redaction of confidential data in the committee papers for TA926, the EAG does not know how either the 88% or the 30% figures compare to the other estimates considered by the committee in TA926. However, this scenario analysis does demonstrate that reducing the proportion of patients having pharmacological BSC (in both arms) has an upward effect on the ICER, albeit one that is much smaller than the downward effect on the

ICER associated with reducing pharmacological BSC usage in the ritlecitinib arm relative to the BSC arm (see Table 2).

Due to the uncertainty described earlier regarding how the cost of pharmacological treatments for patients receiving BSC for severe AA have been estimated, and uncertainty regarding the proportion of patients receiving pharmacological treatment within BSC, the EAG considers the scenarios in Table 2 as illustrative of the potential impact of including pharmacological treatments within BSC under different assumptions, rather than as robust ICERs for decision making. However, the analyses do indicate that incorporating some costs for pharmacological BSC in both arms has much less impact on the ICER than assuming that usage of pharmacological treatments is lower in patients previously treated with ritlecitinib.

Table 2 Scenarios exploring the impact of assuming BSC costs apply in both arms but at varying rates (full population aged >12 using average baseline characteristics i.e. not weighted by age or AU/AT severity)

Source of BSC treatment mix	Proportionate difference between arms [a]	10 years of BSC	2 years of BSC
No pharmacological BSC	NA	£28,633	£28,633
Adelphi DSP (88% have pharmacological BSC)	0%	£24,371	£27,726
	25%	£14,158	£25,553
	50%	£3,946	£23,381
	75%	Dominates	£21,207
UK KOL (87% have pharmacological BSC)	0%	£23,213	£27,480
	25%	£10,227	£24,717
	50%	Dominates	£21,954
	75%	Dominates	£19,191
Adelphi DSP – but with only 30% having pharmacological BSC in both arms	0%	£27,180	£28,324
UK KOL – but with only 30% having pharmacological BSC in both arms	0%	£26,764	£28,235

[a] *this is the proportion by which pharmacological BSC is lower in patients starting BSC after ritlecitinib versus those starting BSC in the BSC only arm.*

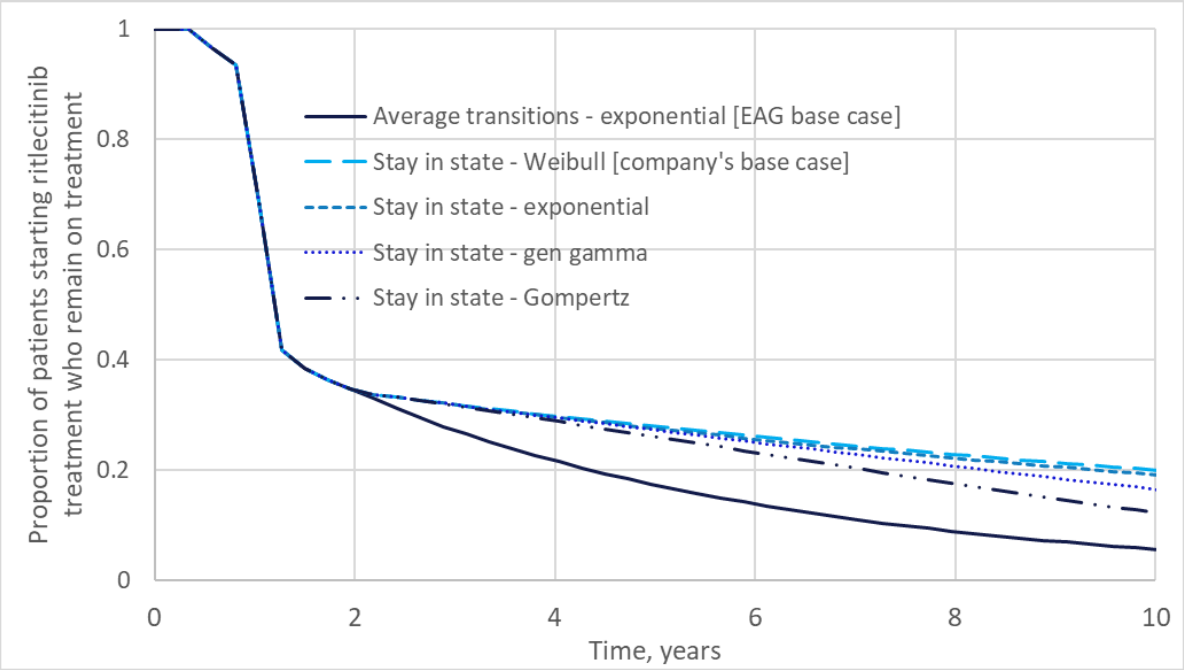
3.4 Additional scenarios on treatment waning and discontinuation

The company disagrees with the committee's preference to assume that treatment efficacy beyond the trial period is best estimated by using the average transition matrix from the second year of the trial as

used in the EAG's base case. The company prefers to assume that patients who remain on treatment will remain in the same SALT score defined health state indefinitely (i.e. steady state). The company has provided several scenarios in which it combines this assumption of no treatment waning with various different curves to extrapolate discontinuation in those who continue to respond to treatment. These curves were provided previously in response to Issue 6 at technical engagement. The EAG notes that it has been able to verify that the ICERs reported by the company (DGD response, Table 11)[2] can be replicated by selection of the appropriate options within the company's submitted model.

The EAG has provided a plot of the proportion of patients remaining on treatment according to the EAG base case, the company base case, and the various scenarios presented by the company (see Figure 1). The main factor causing a difference between the time on treatment extrapolations between the company and the EAG's approach is the choice between assuming a steady state or average transitions for patients remaining on treatment, rather than the choice of discontinuation curve. This can be seen by comparing the EAG's base case, which assumed an exponential time to discontinuation curve, with the company's scenario including the same exponential distribution,

Figure 1 Proportion of patients remaining on ritlecitinib under different assumptions regarding treatment waning (steady state or average transitions) and discontinuation in those who continue to respond (various parametric extrapolations)



The EAG notes that no new evidence has been submitted by the company to support its steady state assumption and the EAG refers the committee to its previous critique of the company's response to Issue 3 at technical engagement. The EAG also notes that the company has not provided any new

evidence on the choice of extrapolation curve in its DGD response and the EAG therefore refers the committee to its previous critique of the company's response to technical engagement issue 6. Given the lack of any new evidence that is relevant to these issues, the EAG has not updated its preferred base case scenario to include any of alternative options modelled by the company.

4. EAG's updated base case scenario

4.1 Description of the EAG's additional analyses

The EAG has updated its base case to include the utility values from Vañó-Galván *et al.*,[4] which is the full-text publication of the same study reported in abstract form by Bewley *et al.*,[5] which the committee previously concluded was the most appropriate source of utility values. However, it has also provided a scenario analysis using results from the ALLEGRO-LT study at 24 months,[2] as this approach is consistent with the reference case and this scenario was requested by the committee (DGD section 3.23)[1].

4.2 Deterministic base case results for the EAG's updated base case

The deterministic base case results for the EAG's updated base case are shown in Table 3. It can be seen that the ICERs for both age subgroups (adolescents and adults) are under £30,000 per QALY. Therefore, the weighted average will be 30,000 per QALY regardless of the proportion of patients who are assumed to be adolescents. Whilst the average ICER may be overestimated if a greater proportion of patients with severe AA are adolescents, as suggested by the company (DGD response, p35), the EAG note that it will not be below £25,000 per QALY under the EAG's preferred assumptions, even if treatment is restricted only to adolescents.

Table 3: Results of the EAG's updated base case analysis for the whole cohort (≥ 12 years) and the age subgroups (12-18 years and ≥ 18 years) [a]

Option	QALYs	Costs	Incremental		ICER
			QALYs	Costs	
Unweighted by AT/AU prevalence or age [b]					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	£28,367
Subgroup aged 12-18 years subgroup					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	£25,665
Subgroup aged ≥ 18 years					

Option	QALYs	Costs	Incremental		ICER
			QALYs	Costs	
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	£29,936
Whole population when using weighted outcomes average across the age categories and assuming 4.91% of patients with severe AA are aged 12-17 years					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	£29,679

[a] *Deterministic ICERs*

[b] *This is for the whole cohort using average baseline characteristics and efficacy data pooled across the whole cohort and does not represent the committee's preference for weighting the average outcomes for young people and adults in the model separately*

Table 4 shows the results for the same EAG preferred scenario for subgroups defined according to whether patients have AT/AU and when using a weighted average across patients with and without AT/AU. It can be seen that taking a weighted average across those with and without AT/AU, brings the average ICER down, compared to using average baseline characteristics, because those with AT/AU were over-represented in the ALLEGRO 2b/c trial and the ICER was higher for this subgroup.

Table 4: EAG's updated base case analysis for subgroups with and without AT/AU and weighted average across the whole cohort [a]

Option	QALYs	Costs	Incremental		ICER
			QALYs	Costs	
Unweighted by AT/AU prevalence or age [b]					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	£28,367
AT/AU subgroup					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	£36,378
Non-AT/AU subgroup					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	£24,790
Whole cohort using weighted average approach across the AT/AU and non-AT/AU subgroups and the proportion with AT/AU estimated by the company (9.52%)					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	£25,406

[a] *Deterministic unless otherwise stated; does not use weighted average across age subgroups approach as this is not available for the AT/AU and non-AT/AU subgroups*

4.3 Probabilistic results for the EAG's updated base case

The EAG were unable to generate probabilistic sensitivity analysis (PSA) results for the subgroups with and without AT/AU. Therefore, the probabilistic results are provided for the age subgroups only. The results in Table 5 are within 2% of the deterministic results (Table 3) for each age subgroup. These results suggest that the model is fairly linear and the deterministic results provide a good approximation for the results expected when using average outcomes from the PSA. When using a weighted average across age subgroups, the ICER is £30,407 per QALY across the whole cohort. It is not possible to estimate the proportion of PSA samples that provide an ICER under £30,000 when using a weighted average approach as the model has to be run independently for each age group and the PSA samples are not correlated across runs.

Table 5 EAG's updated base case results when using the probabilistic sensitivity analysis [a]

Option	QALYs	Costs	Incremental		ICER
			QALYs	Costs	
Subgroup aged 12-18 years subgroup					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	£26,199
Subgroup aged ≥ 18 years					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	£30,678
Whole population when using weighted outcomes average across the age categories and assuming 4.91% of patients with severe AA are aged 12-17 years					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	£30,407

[a] *The EAG were unable to generate PSA results for the AT/AU and non-AT/AU subgroups.*

4.4 Deterministic results for the scenario analysis including EQ-5D from ALLEGRO LT

The results using the utility values by health state obtained from the ALLEGRO LT data at 24 months (Table 6) provide an ICER of £97,100 for the adolescent subgroup, with all other ICERs being in excess of £100,000 per QALY. The weighted average ICER when using the age subgroups is £150,918 per QALY, whilst the weighted average using the AT/AU based subgroups is £130,335 per QALY. The EAG has not run the probabilistic analysis for this scenario, but it is clear that the probabilistic ICERs are likely to exceed £30,000 per QALY if the data from ALLEGRO LT are considered to provide the most appropriate estimates of utility by SALT score.

Table 6 EAG deterministic scenario analysis using EQ-5D from ALLEGRO LT

Option	QALYs	Costs	Incremental		ICER
			QALYs	Costs	
Whole cohort unweighted by AT/AU prevalence or age [a]					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	£142,860
Subgroup aged 12-18 years subgroup					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	£97,100
Subgroup aged ≥ 18 years					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	£155,655
Whole cohort when using weighted outcomes average across the age categories and assuming 4.91% of patients with severe AA are aged 12-17 years					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	£150,918
AT/AU subgroup					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	£174,759
Non-AT/AU subgroup					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	£127,659
Whole cohort using weighted average approach across the AT/AU and non-AT/AU subgroups and the proportion with AT/AU estimated by the company (9.52%)					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	£130,335

[a] *This is for the whole cohort using average baseline characteristics and efficacy data pooled across the whole cohort and does not represent the committee's preference for weighting the average outcomes for young people and adults in the model separately*

4.5 Deterministic results for the scenario incorporating pharmacological BSC costs

The EAG has also conducted a scenario analysis using the proportions having pharmacological BSC from the Adelphi DSP (88%), assuming that this proportion is the same across both the ritlecitinib and BSC arms, and that pharmacological BSC lasts for a maximum of 10 years. The EAG has not incorporated any difference in BSC usage across arms as it considers that this lacks face validity (see Section 3.3). However, the EAG considers that the scenario presented in Table 7 still likely overestimates the costs of pharmacological BSC and also fails to capture any possible effectiveness of

these treatments (see Section 3.3). For these reasons, the EAG considers that this scenario provides an estimate that is potentially biased in favour of ritlecitinib, but it could be considered to provide an extreme lower limit on the plausible ICER. As such the EAG considers that the ICER is still likely to be over £20,000 per QALY even if some pharmacological BSC costs are included in both arms.

Table 7 EAG deterministic scenario analysis incorporating pharmacological BSC

Option	QALYs	Costs	Incremental		ICER
			QALYs	Costs	
Whole cohort unweighted by AT/AU prevalence or age [a]					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	£24,145
Subgroup aged 12-18 years subgroup					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	£22,444
Subgroup aged ≥ 18 years					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	£25,342
Whole cohort when using weighted outcomes average across the age categories and assuming 4.91% of patients with severe AA are aged 12-17 years					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	£25,167
AT/AU subgroup					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	£31,469
Non-AT/AU subgroup					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	£20,894
Whole cohort using weighted average approach across the AT/AU and non-AT/AU subgroups and the proportion with AT/AU estimated by the company (9.52%)					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	£21,457

[a] This is for the whole cohort using average baseline characteristics and efficacy data pooled across the whole cohort and does not represent the committee's preference for weighting the average outcomes for young people and adults in the model separately

5. Discussion

Overall, the EAG considers that the psychometric analysis of the EQ-5D outcomes from the ALLEGRO trials is mixed and therefore the EAG still prefers to use the EQ-5D derived estimates of utility from the literature in its base case. The EAG has therefore only updated its base case to include the utility values reported in the full-text publication of the same study previously reported in abstract form and preferred by the committee at the first meeting.[4, 5] The EAG's base case ICERs are therefore very similar to what they were in the previous EAG addendum with deterministic ICERs ranging £25,000 to £30,000 per QALY depending on whether the results are weighted across age subgroups or across patients with versus without AT/AU. The company argues that the model results are conservative because adolescents were under-represented in the ALLEGRO trial (DGD response, pg8).[2] However, the EAG notes that the company's own estimate of the proportion of patients with severe AA who are adolescents is 4.91% which is lower than the proportion who were adolescents in the trial (14.6%) and the company has not provided any alternative higher estimate. In addition, none of the ICERs for adolescents were under £20,000 per QALY when using the EAG's preferred assumptions.

The incorporation of the 24-month EQ-5D data from the ALLEGRO LT study to estimate utility by SALT score substantially increases the ICER, although the EAG notes that this may partially be because the population recruited to the study excluded those with the greatest mental health impacts from AA who may have the greatest capacity to benefit from treatment. This makes sense when considering that Vañó-Galván *et al.* identified the mental health domain as being the EQ-5D domain most affected by AA.[4]

Although the ICERs are under £20,000 per QALY when using the company's vignette study as the source of utility values, the EAG does not consider that any of the additional evidence provided by the company in response to the DGD alters their previous assessment of the validity of the vignette study. The EAG still has reservations regarding the vignette descriptions in addition to new concerns regarding the vignette methodology and therefore the EAG considers that the utility estimates from the vignette study should be treated with caution.

The EAG considers that whilst the inclusion of pharmacological treatments within BSC is likely to reduce the ICER, the most plausible ICER is still likely to be above £20,000 QALY because the EAG preferred to assume the same usage of pharmacological treatments within BSC across both arms. The EAG believes this is reasonable as the company has provided no evidence to demonstrate that the usage of pharmacological treatments will be reduced in those who have stopped ritlecitinib treatment compared with those who were never offered ritlecitinib treatment, when both groups are assumed to have SALT ≥50.

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Appendix 1.

The text describing Figure 1 states both that baseline for the roll-over cohort refers to the "*baseline of the original study (i.e., from ALLEGRO 2b/3*)," and that after 24 months in the ALLEGRO LT study patients have had a total of 30 to 36 months of treatment at 50mg.[2] The latter suggests that Figure 1 shows time since starting ALLEGRO LT, whilst the former suggests that it shows time on treatment since the baseline of ALLEGRO 2b/3. This makes it difficult to know what time period the data shown relate to and some additional clarity from the company on this issue would be useful.

In addition, the numbers at the bottom of Figure 1 suggests the data relate to 523 patients. The EAG believes these are the adult patients from within the 603 roll-over patients (clarification response, Table 7 and ALLEGRO LT CSR, Table 5).[28, 29] But the graph legend also states "*roll-over cohort (N=191)"*.[2] This could simply be a typographical error. However, the number of patients treated with a 50mg dose has previously been described as [redacted] in the plots showing treatment response in ALLEGRO LT (company's TE response to issue 3, Figure 2).[28]

With regards to Figures 3 and 4, the EAG was unable to identify how the 253 modified de novo patients related to the 449 de novo patients reported elsewhere (clarification response Table 7),[28] of which [redacted] were adults (ALLEGRO LT CSR, Table 5).[29] Neither is it clear why the legend says N=502 when the numbers below the graph show N=253. However, N=502 has previously been given as the number of patients having 200mg/50mg in the ALLEGRO LT study (company's TE response to issue 3, Figure 1).[28] The company has previously defined a modified de novo group for ALLEGRO LT as excluding those with known androgenetic alopecia or a screening or baseline SALT score ≤ 50 (clarification response B1).[28] So these factors may explain the reduction from [redacted] adults to the 253 individuals presented, but again, the EAG is unclear if this is the case.

Overall, the EQ-5D data from ALLEGRO LT appear to be presented for a different cohort from that used to present long term response to ritlecitinib in the company's technical engagement response and some additional clarity from the company on the exact cohorts presented in these figures would be useful.

Appendix 2

Table 8: Company's base case analysis for the whole cohort (≥ 12 years), subgroups (age and AT/AU status) and whole cohort when using weighted averages across subgroups [a]

Option	QALYs	Costs	Incremental		ICER
			QALYs	Costs	
Whole cohort unweighted by AT/AU prevalence or age [b]					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	£8,294
Subgroup aged 12-18 years subgroup					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	£8,940
Subgroup aged ≥ 18 years					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	£7,986
Whole cohort when using weighted outcomes average across the age categories and assuming 4.91% of patients with severe AA are aged 12-17 years					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	£8,026
AT/AU subgroup					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	£9,900
Non-AT/AU subgroup					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	£7,617
Whole cohort using weighted average approach across the AT/AU and non-AT/AU subgroups and the proportion with AT/AU estimated by the company (9.52%)					
BSC	[redacted]	[redacted]			
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	£7,733

[a] *Deterministic unless otherwise stated*

[b] *This is for the whole cohort using average baseline characteristics and efficacy data pooled across the whole cohort and does not represent the committee's preference for weighting the average outcomes for young people and adults in the model separately*