National Institute for Health and Care Excellence

Health Technology Evaluation

Ritlecitinib for treating moderate to severe alopecia areata in people 12 years and over ID4007
Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE 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 submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Pfizer	Yes, it is appropriate to consider ritlecitinib within a single technology appraisal (STA)	Comment noted. No action needed.
	British Association of Dermatologists	There is a lifetime incidence of this disorder of 2.1% and point prevalence of 0.58% of the adult population. Children and young people are also frequently affected. Alopecia areata (AA) effects women and men equally and incidence has been linked to social deprivation and is more common in non-Caucasian ethnicities. The frequency of disease, and social and mental health impact warrant further NICE appraisals to evaluate treatments for this underserved patient group. Currently, there is paucity of robust/highly effective treatments for this condition.	Comment noted. No action needed.
	Alopecia UK	An effective treatment for alopecia is much needed	Comment noted. No action needed.

Section	Stakeholder	Comments [sic]	Action
Wording	Pfizer	Please change “” [redacted] to “ [redacted]	Comment noted. Because the marketing authorisation has not yet been received, the wording has been kept broad to align with the population of the ALLEGRO-LT clinical trial. No action needed.
	British Association of Dermatologists	The background may benefit from additional, more recent referencing.	Comment noted. Additional references have been added.
	Alopecia UK	Yes - From a patient organisation perspective we ask that psychosocial impact of alopecia is assessed as much as % hair loss	Comment noted. Health-related quality of life is listed as an outcome in the scope which includes measures of psychological impact. No action needed.
Additional comments on the draft remit	Pfizer	NA	No action needed.
	British Association of Dermatologists	Currently, there are no licensed treatments beyond topical steroids for AA. There is a significant mental health burden associated with this hair loss disorder and current treatments are messy, or painful, or unlicensed, and/or require travel to dermatology centres weekly for contact immunotherapy.	Comment noted. No action needed.

Section	Stakeholder	Comments [sic]	Action
		Inclusion of children (12+) and young adults in the appraisal is particularly important as AA commonly first presents in childhood, has a poorer prognosis and is more challenging to treat with standard therapies. Effective therapy for this group is urgently needed to minimise cumulative life course impairments resulting from being affected by AA, allowing those affected to attain their full potential in life. Duration of AA may also impact long-term prognosis, so access to effective therapy early in the disease course in this group is important.	
	Alopecia UK	NA	No action needed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Pfizer	<u>First paragraph</u> Please clarify that alopecia areata also affects the scalp. We propose changing *"It can affect any hair-bearing skin such as the beard, eyebrows, eyelashes, body and limbs"* to *"It can affect any hair-bearing skin such as the **scalp,** beard, eyebrows, eyelashes, body and limbs"* <u>Second paragraph</u> Please change "In the UK, it is estimated that approximately 0.6% of adults have alopecia areata" to *"In the UK, it is estimated that approximately 0.58% of adults have alopecia areata" and clarify that the relevant source for this information is number 4 in the reference list"*	Comment noted. Wording in paragraph 1 has been updated to include 'scalp'. Wording in paragraph 2 has been updated to state '0.58%'. Reference 4 has been added.

Section	Consultee/ Commentator	Comments [sic]	Action
		Reference: Harries M, Macbeth AE, Holmes S, Chiu WS, Gallardo WR, Nijher M, de Lusignan S, Tziotzios C, Messenger AG (2022) The epidemiology of alopecia areata: a population-based cohort study in UK primary care. Br J Dermatol 186(2):257-265. Third paragraph Please change *"Spontaneous remission within one year is seen in up to 80% of people with limited patches of hair loss of less than one year duration.[1] When hair loss becomes extensive, spontaneous re-growth is rare"* to "*Spontaneous remission within one year is seen in up to 80% of people with limited patches of hair loss of less than one year duration.[1] However hair pattern regrowth is variable and unpredictable and when hair loss becomes extensive, spontaneous re-growth is rare."* *Reference: Harries MJ, et al. Management of alopecia areata. BMJ. 2010;341:c3671* Fourth paragraph – licensed treatment options Please clarify that there are no licensed **systemic** treatment options for patients with alopecia areata Fourth paragraph – treatment pathway In the absence of up-to-date guidelines or published treatment pattern studies, we appreciate the uncertainty around the treatment pathway for severe alopecia areata in the UK. Of the treatments listed within the scoping document for ritlecitinib, research with 8 clinicians in the UK suggests that treatment options used for severe (≥50% hair loss) alopecia areata include	Wording in paragraph 3 has been updated as suggested. Baricitinib received CHMP positive opinion in May 2022 and marketing authorisation in June 2022. Because of this, a sentence on "no licensed systemic treatment options" has not been added to the scope.

Section	Consultee/ Commentator	Comments [sic]	Action
		topical (or in some cases intralesional) corticosteroids, contact immunotherapy (although it is not widely available), oral corticosteroids (most commonly prednisolone, although for <3 – 6 months) and immunosuppressants (methotrexate, azathioprine, MMF & ciclosporin). Topical/oral minoxidil can be used alongside oral corticosteroids or immunosuppressant therapies although it was less commonly reported to be used as monotherapy. We will provide more insights into this research within the appraisal process. <u>Fifth paragraph</u> Please add the mechanism of action for ritlecitinib to be consistent with the baricitinib draft scope. Proposed wording is provided below. "*Ritlecitinib (brand name pending, Pfizer Ltd) is a selective and irreversible inhibitor of Janus kinase 3 (JAK 3) and the tyrosine kinase expressed in the hepatocellular carcinoma (TEC) family. JAKs are enzymes that mediate the transduction of intracellular signals involved in the process of inflammatory disease. Tyrosine kinase is an enzyme that functions as an "on" or "off" switch in many cellular functions. Ritlecitinib is administered orally.*" <u>Additional comment</u> Please add an additional paragraph to describe the psychosocial burden associated with AA. We propose*:* *"The burden of AA extends beyond hair loss and can completely change patients' appearances and their self-perception. For some, hair loss is emotionally challenging, resulting in higher incidences of psychosocial impacts in patients with AA (well-documented within the literature) compared to healthy controls such as negative effects on self-esteem, social interactions, and health-related quality of life (HRQoL)."*	Information provided on current treatments based on research with UK clinicians has been noted and will be considered within the appraisal process. The ritlectinib scope has been written using the new scoping template. Based on this new template, details of mechanisms of action are not included within the scope. No action needed. A sentence has been added to the scope to briefly describe mental health considerations. However, the background section within the scope is

Section	Consultee/ Commentator	Comments [sic]	Action
		References: • *Messenger AG, et al. British Association of Dermatologists' guidelines for the management of alopecia areata 2012. Br J Dermatol. 2012;166(5):916-926.* • *Harries MJ, et al. Management of alopecia areata. BMJ. 2010;341:c3671.* • *Fricke VAC, Miteva M. Epidemiology and burden of alopecia areata: a systematic review. Clin Cosmet Investig Dermatol. 2015;8:397-403.* • *Strazzulla LC, et al. Alopecia areata: Disease characteristics, clinical evaluation, and new perspectives on pathogenesis. J Am Acad Dermatol. 2018;78(1):1-12.* • *Xu L, et al. A Practical Approach to the Diagnosis and Management of Hair Loss in Children and Adolescents. Front Med (Lausanne). 2017;4:112.* • *Aldhouse NVJ, et al. "'You lose your hair, what's the big deal?' I was so embarrassed, I was so self-conscious, I was so depressed:" a qualitative interview study to understand the psychosocial burden of alopecia areata. J Patient-Rep Outcomes. 2020;4(1):1-12.* • *Tan E, et al. The pattern and profile of alopecia areata in Singapore – a study of 219 Asians. Int J Dermatol. 2002;41(11):748-753.*	generally kept broad. Additional disease burden (such as psychosocial burden) can be discussed within the company submission for consideration by the committee. No action needed.
	British Association of Dermatologists	The background section includes a recent epidemiology reference, but some aspect could be expanded, and the other references updated, as outlined below: The background section includes the recent UK epidemiological studies (Harries *et al.* https://onlinelibrary.wiley.com/doi/10.1111/bjd.20628) that	Comment noted. The reference for the epidemiological data has been updated within the scope. Further epidemiological considerations (such as

Section	Consultee/ Commentator	Comments [sic]	Action
		estimates the current (2018) point prevalence of AA in UK adults. However, this estimate is incorrectly referenced in the text (currently listed under reference 5). It should be noted that these data were derived from interrogation of a large primary care database (RCGP-RSC) and therefore rely on individuals with AA presenting to primary care. This may underestimate the total prevalence in the UK population. This paper also includes detailed information on age of onset, risk groups (e.g., more frequently in those of Asian background, and from socially deprived and urban areas), as well as referral rates. The increased prevalence in ethnic minority and deprived populations may be underestimated as these groups may be less likely to present to health services. These factors are only partially explored in the background section. Clinical diagnosis is also made by identifying circular patches of hair loss or typical ophiasis patterns and, in some cases, identifying whitening of the hairs, in addition to the exclamation mark hairs described. Treatment of AA of less than 50% surface area with topical corticosteroids in primary and secondary care is commonplace. With single patches of hair loss, watchful waiting is likely to result in spontaneous regrowth in 80% of cases, but with increasing extent of disease, spontaneous regrowth becomes much less likely. There is also some clinical evidence to suggest that early treatment for smaller patches with topical or intralesional steroids may possibly reduce progression of disease, although this is yet to be proven in good quality clinical trials. There is a brief comment on disease associations with AA, including higher rates of atopic disease and autoimmune conditions, but this is referenced incorrectly. Data on these associations should shortly be available from the	increased prevalence in specific populations) will be considered during the appraisal process. Comment noted. The background section has been updated to note that in some cases, identifying whitening of the hairs can also aid diagnosis. Patterns of hair loss is already captured within this paragraph. Comment noted. The reference for this statement has been

Section	Consultee/ Commentator	Comments [sic]	Action
		RCGP-RSC series of studies currently underway (Harries *et al.* https://bmjopen.bmj.com/content/bmjopen/11/11/e045718.full.pdf for protocol of this work). There is no mention of the impact of AA on mental health. Higher rates of anxiety and depression are seen in this population (Macbeth *et al.* https://onlinelibrary.wiley.com/doi/10.1111/bjd.21055). Interestingly, there appears to be a "two-way street" between AA and depression development. Higher rates of time off work and unemployment are also seen in the disease group. In terms of pathogenesis, AA is generally agreed to be an inflammatory autoimmune T cell-mediated disease directed against hair follicles. Genetic predisposition has been shown through GWAS study (Petukhova *et al.* https://pubmed.ncbi.nlm.nih.gov/20596022/). Immune privilege collapse of the HF bulb, and NKG2D+ cell infiltration are key processes at play. It would be worth acknowledging the AA Priority Setting Partnership that highlights AA uncertainties important to both clinicians and patients (Macbeth *et al.* https://onlinelibrary.wiley.com/doi/10.1111/bjd.15099). Finally, comment on the impact and disease burden of AA in relation to other conditions could be included (Karimkhani *et al.* https://onlinelibrary.wiley.com/doi/10.1111/bjd.13559 and Korta *et al.* https://pubmed.ncbi.nlm.nih.gov/29548423/). Additional references for consideration to improve this section include:	checked and an additional reference has been included. Comment noted. A sentence has been included to mention potential impact on mental health. However, the background section within the scope is generally kept broad. Additional factors will be considered during the appraisal process.

Section	Consultee/ Commentator	Comments [sic]	Action
		Prognosis Ikeda https://pubmed.ncbi.nlm.nih.gov/5864736/ Impact on quality of life Liu *et al.* https://pubmed.ncbi.nlm.nih.gov/29425723/	
	Alopecia UK	NA	No action needed.
Population	Pfizer	Please change to "People aged 12 years and over with severe alopecia areata"	Comment noted. The wording has been kept broad to align with the population of the ALLEGRO-LT clinical trial. No action needed.
	British Association of Dermatologists	The population is appropriate, and importantly includes children (12+). Moderate-to-severe AA would need to be defined in terms of SALT score.	Comment noted. Definition of the population groups will be considered in further detail during the appraisal process. No action needed.
	Alopecia UK	NA	No action needed.
Subgroups	Pfizer	Please clarify what is meant by *"type of alopecia areata" in relation to potential subgroups.*	Comment noted. The wording in the subgroup section has been updated to provide

Section	Consultee/ Commentator	Comments [sic]	Action
			examples of types of alopecia areata.
	British Association of Dermatologists	The subgroup description does not include duration of disease. The current trial data only included those with "fixed hair loss of 7 years or less in duration" (King et al. https://pubmed.ncbi.nlm.nih.gov/33757798/). Longer disease durations may have a poorer treatment response and therefore this may be important in stratifying patients when deciding treatment. Eyebrow, eyelash, beard, and nail involvement with significant functional or psychological impact should also be considered.	Comment noted. The impact of disease durations will be considered during the appraisal process. No action needed.
	Alopecia UK	NA	No action needed.
Comparators	Pfizer	No comment	No action needed.
	British Association of Dermatologists	Currently accepted UK treatment for AA is very variable and is clinician-dependant. In specialist centres, contact immunotherapy may be considered a helpful comparator but this is only available in limited dermatology centres. Various treatments are available. See the expert consensus paper published recently that summarises the main options (Meah *et al.* https://pubmed.ncbi.nlm.nih.gov/32165196/). This paper is useful as the current quality of evidence for most AA therapies is poor.	Comment noted. No action needed.
	Alopecia UK	NA	No action needed.
Outcomes	Pfizer	No comment	No action needed.
	British Association of Dermatologists	AA hair-loss assessment is generally done by the % extent of hair loss – usually using the Severity of Alopecia Tool (SALT) score. **SALT outcomes can be expressed in different ways including absolute SALT score or % reduction in surface area affected.**	Comment noted. Specific assessment tools are not generally included within scoping

Section	Consultee/ Commentator	Comments [sic]	Action
		Certain hair loss sites may have a disproportionate impact on an individual (e.g. beard or eyebrow loss), or more limited patches may be in an area more difficult to camouflage (e.g. frontal hairline). The main hair loss sites to consider are scalp, eyebrows, and eyelashes. However, beard hair loss should also be considered specifically as this can have religious implications, e.g. in the Sikh and Jewish faiths. **[N.B. For disease severity, SALT would only be applicable for scalp AA.]**	documents. No action needed.
	Alopecia UK	NA	No action needed.
Equality	Pfizer	There are currently no licensed systemic treatment options for patients with severe hair loss in the UK. Contact immunotherapy, which may be used prior to systemic treatment options, requires multiple clinical visits over several months and it is not widely available in the UK, thus resulting in inequality of access. Further, there is a disparity in wig provision across NHSE with local NHS organisations setting limits on the number of wigs available to patients. This further exacerbates the inequity in access to treatment. In addition to the disparity in wig provision, not all patients are able to wear wigs comfortably - an example is patients with alopecia who also need to wear hearing aids; these patients can find it difficult to get wigs to fit properly and also experience a rustling sound when the wig is next to the ears. The frequency of AA is also higher for people with skin of colour, particularly for those of Asian backgrounds where it can be more than three times more common than in Caucasians (IRR Asian vs white ethnicity: 3.32 [95% CI: 3.11, 3.55]). People from more deprived backgrounds living in urban areas	Comment noted. These issues have been captured within an Equality Impact Assessment. Where appropriate and relevant, the committee will consider these potential equality issues during the decision-making process.

Section	Consultee/ Commentator	Comments [sic]	Action
		are also more likely to have AA and are less likely to be able to pay for higher quality wigs, where these are not accessible. *References:* • *Harries M, Macbeth AE, Holmes S, Chiu WS, Gallardo WR, Nijher M, de Lusignan S, Tziotzios C, Messenger AG (2022) The epidemiology of alopecia areata: a population-based cohort study in UK primary care. Br J Dermatol 186(2):257-265.* • *Alopecia UK. Current Challenges in the Human Hair Wig Market. 2021. at* NHS England Wig Report | Alopecia UK • 'Am I the only one with hearing aids and alopecia?' - BBC News	
	British Association of Dermatologists	Having a disease duration cut-off of 7 years will indirectly lead to possible age-discrimination as those with longer duration of disease are likely to be older. Meah *at al.* https://pubmed.ncbi.nlm.nih.gov/32926985/ expert consensus report *"Hair loss can become irreversible when AA persists for 10 years but should not be assumed to be so or contraindicate a trial of therapy"*. Epidemiological data has shown that AA is more common in those of Asian background and those of lower socioeconomic status and urban location, but referral to secondary care is lower in these lower socioeconomic groups (Harries *et al.* https://onlinelibrary.wiley.com/doi/10.1111/bjd.20628). Inclusion of individuals with these characteristics is important in the clinical and cost-effectiveness data and in the patient representation in the consultation process. Beard hair loss can have some religious implications, e.g. some from the Sikh and Jewish faiths. Here, many standard treatments are more challenging for	Comment noted. These issues have been captured within an Equality Impact Assessment. Where appropriate and relevant, the committee will consider these potential equality issues during the decision-making process. It is noted that the information in the trial database shows that the key trial populations include people with

Section	Consultee/ Commentator	Comments [sic]	Action
		beard hair loss, where systemic medication is often required at an earlier stage. Some health-related quality of life measures may not adequately capture the impact of living with health conditions in older people (questions about work, studying, sport) or those who are not in a relationship (question about sexual activity); they may also not capture anxiety and depression across all groups – two parameters that are commonly and negatively influenced by AA. Additionally, they may discriminate against those who are non-native English speakers	disease duration up to 10 years. The population with the disease duration included in the key trials has been discussed in the Equality Impact Assessment.
	Alopecia UK	NA	No action needed.
Other considerations	Pfizer	No comments	No action needed.
	British Association of Dermatologists	No further comments.	No action needed.
	Alopecia UK	NA	No action needed.
Questions for consultation	Pfizer	No comments	No action needed.
	British Association of Dermatologists	**Where do you consider ritlecitinib will fit into the existing care pathway for alopecia areata?** There are no licensed treatment specific for AA. JAK inhibitors in general would fit at the stage when (unlicensed) topical contact immunotherapy (if available) is considered, i.e. ≥50% hair loss that has not responded to topical +/- oral corticosteroids and intralesional corticosteroids (where appropriate). N.B. topical contact immunotherapy can only treat *scalp* hair loss.	Comments noted. The extent to which ritlectinib is innovative ritlectinib and the potential for managed access etc. will be considered by the committee during the

Section	Consultee/ Commentator	Comments [sic]	Action
		See also the expert consensus report (Meah *et al.* https://pubmed.ncbi.nlm.nih.gov/32165196/). Consensus was achieved for the following statement regarding preferred second-line agents for AA "If all treatments were equally reimbursed, JAK inhibitors would be the ideal choice for systemic therapy in adults". **Which types of alopecia areata would ritlecitinib be considered for?** Usually, this treatment would be considered in Moderate-severe AA >50% scalp area, including AT/AU However, treatment may be considered in more limited AA, or extra-scalp AA unresponsive (or intolerant) of standard therapies, particularly if psychological impact is prominent. It should be noted that there is a move towards a more holistic approach to defining AA severity beyond just % scalp involvement (see King et al. Defining severity of alopecia areata. Dermatol Therapy 2022; 12: 825-34). This introduces the concept of a multidimensional framework to assess AA severity. **Would ritlecitinib be a candidate for managed access?** Possibly; this would be useful to help shape and inform its long-term use as it is still unclear who will achieve complete remission, who may need just dose reduction for maintenance, etc. It would depend on what additional information is required before the treatment is approved. This approach may answer questions about demand and test eligibility criteria but is unlikely to answer longer term questions about efficacy, safety, patient stratification and treatment duration – this will be best answered by a national AA pharmacovigilance registry (N.B. Funding for a national AA register from the	appraisal process. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		British Skin Foundation has been awarded, with platform build starting this year. The register will be hosted at the University of Manchester and hopefully administered by the British Association of Dermatologists). **Do you consider ritlecitinib to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?** JAK inhibitors are innovative in their use for AA and may make a significant impact on this patient group, as currently the treatment of severe AA is very difficult. There are no evidence-based treatments available on the NHS that have been evaluated successfully in high-quality clinical trials, except for topical corticosteroids, which are usually ineffective in severe disease. Those with AA have a significant mental health burden associated with their disease and hopefully availability of evidence-based treatments will possibly improve the mental health burden, although this is yet to be proven in clinical trials. AA is also associated with time away from work, which will have a significant economic impact on the wider population. Current available therapies for AA are often ineffective. Regular clinic visits, blood monitoring and drug costs, along with wig prescription and wider societal issues (e.g. unemployment) all contribute the impact of AA on the individual, NHS and society more widely. Effective treatment options are needed urgently to prevent the longer term sequalae of ongoing AA (e.g. mental health issues).	

Section	Consultee/ Commentator	Comments [sic]	Action
		Do you consider that the use of ritlecitinib can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? It is difficult to truly capture the impact of treatments for AA using QALYs, as this may not question all the domains relevant to our patient population; perhaps another measure may need to be considered. Further, RCT inclusion/exclusion criteria may exclude participants with significant co-morbidities, including mental health impact, which may skew the utility value coming from RCT data. **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** It is difficult to know the best way to capture disease impact in the AA population. Poor quality of life, anxiety and depression can be prominent in this group. There are a number of disease specific quality of life tools now available (e.g. AASIS – Winnette *et al.* https://pubmed.ncbi.nlm.nih.gov/35000236/). The disease burden of AA in relation to other conditions is explored in these publications (Karimkhani et al. https://onlinelibrary.wiley.com/doi/10.1111/bjd.13559 and Korta et al. https://pubmed.ncbi.nlm.nih.gov/29548423/).	
	Alopecia UK	-	No action needed.
Additional comments on the draft scope	Pfizer	To address the reference to a Multiple Technology Appraisal (MTA) in the draft scope list of questions, we do not think that this is necessary or appropriate for ritlecitinib. We would encourage NICE to engage directly with Pfizer if this is something that is being explored in the future.	Comment noted. This topic is currently routed to Single Technology Appraisals. If further

Section	Consultee/ Commentator	Comments [sic]	Action
			discussion is required, NICE will engage directly with the company.
	British Association of Dermatologists	NA	No action needed.
	Alopecia UK	NA	No action needed.