National Institute for Health and Care Excellence

Single Technology Evaluation

Baricitinib for treating severe alopecia areata [ID3979]

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	British Association of Dermatologists (endorsed by the Royal College of Physicians)	This request for appraisal is appropriate as there is a lifetime incidence of this disorder of 2.1% and point prevalence of 0.58% of the adult population. Alopecia areata (AA) effects women and men equally and incidence has been linked to social deprivation. The frequency of disease, and social and mental health impact warrant further NICE appraisals to evaluate treatments for this underserved patient group.	Comments noted. No action required.
	Eli Lilly and Company	Yes, this is an appropriate topic to refer to NICE for Single Technology Appraisal.	Comment noted. No action required.
Wording	British Association of Dermatologists (endorsed by the Royal College of	Wording is appropriate.	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Physicians)		
	Eli Lilly and Company	Yes, the remit broadly reflects the clinical and cost effectiveness for baricitinib in severe AA.	Comment noted. No action required.
Timing Issues	British Association of Dermatologists (endorsed by the Royal College of Physicians)	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, or require travel to dermatology centres weekly for contact immunotherapy.	Comments noted. No action required.
	Eli Lilly and Company	There is no timing issue foreseen for this appraisal.	Comment noted. No action required.
Additional comments on the draft remit	Eli Lilly and Company	None.	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	British Association of Dermatologists (endorsed by the Royal College of	The background section appears outdated and many of the supporting references are old. More accurate UK data on epidemiology of AA is now available from UK epidemiological studies (Harries *et al.* https://onlinelibrary.wiley.com/doi/10.1111/bjd.20628). These data were derived from interrogation of a large primary care database (RCGP-RSC) and	Comments noted. This section of the scope aims to provide a brief overview of the technology for the evaluation; additional

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	Physicians)	therefore rely on individuals with AA presenting to primary care. This may underestimate the total prevalence in the UK population. This paper includes 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. 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 no comment on disease associations with AA, including higher rates of atopic disease and autoimmune conditions. Data on these associations should shortly be available from the 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 emotional impact of AA. 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. More information on prognosis would be helpful. Although many with limited, patchy disease may regrow their hair, this reported spontaneous regrowth	details may be considered by the committee, if appropriate, at the time of the evaluation. Some of the suggested amendments have been included in the scope.

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		rate drops significantly in those attending secondary care. Extent and duration of hair loss, as well as age of onset are key factors. Possible references to review include Ikeda https://pubmed.ncbi.nlm.nih.gov/5864736/ and Tosti *et al.* https://pubmed.ncbi.nlm.nih.gov/16908349/. From these references it shows a progressive tendency to more extensive hair loss and worse prognosis in AA over time. 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/).	
	Eli Lilly and Company	This section broadly captures the background information of AA, however Lilly would propose that the following important points be additionally incorporated into this section: 1) AA can lead to a rapid and profound distortion of appearance.[1] It is important to note that the clinical presentation of AA differs from other conditions, especially alopecia androgenetica (pattern baldness). 2) The scalp is affected in 90% of cases of AA.[2] In practice, severity classification and clinical management is currently driven by the extent of	Comments noted. This section of the scope aims to provide a brief overview of the technology for the evaluation; additional details may be considered by the committee, if appropriate, at the time of the evaluation. Some

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		scalp hair loss.[3] 3) The psychological impact and consequent effects on health-related quality of life (HRQoL) are important aspects of AA. Hair loss in visible areas is reported by patients to be the most troublesome aspect of AA and the primary cause of their distress.[4-6] Multiple studies have shown that AA may have a significant negative impact on HRQoL and result in higher levels of anxiety and a greater risk of depression.[7, 8] It has been shown in a recent UK study that adults newly diagnosed with alopecia areata (n=5,435 in UK primary care) have 30–38% higher risk of being subsequently diagnosed with new onset depression and anxiety.[9] Quality of life impairment and psychological burden are important considerations for the therapeutic management of patients with AA.[10, 11] 4) AA is characterised by an immune-mediated attack on hair follicles, which leads them to change from growth (anagen) phase into premature regression (catagen) phase.[1] 5) The evolution of AA is unpredictable, and the prognosis varies highly depending on the severity and duration of the disease. Spontaneous hair re-growth has been reported to be frequent at the beginning of the disease when most patients have mild forms of AA.[12, 13] When hair loss becomes extensive, it tends to be chronic and spontaneous re-growth is rare. Consequently, the prognosis of patients with severe AA is considered to be poor.[10, 14] 6) Assessment of efficacy difficult in AA, especially in the absence of a control group, or when participants with various degrees of disease severity have been included. Topical and intralesional corticosteroids are the first-line treatments recommended for mild AA.[10] The standard of care in severe AA	of the suggested amendments have been included in the scope.

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		(such as it is) currently involves trialling off-label treatments that have not been well evaluated in clinical trials and which do not have marketing authorisations for this disease.[10] The overall efficacy of such treatments seems particularly low for patients with severe AA.[10] Moreover, some treatment options can be uncomfortable for the patient, time consuming, and associated with side effects which limit their long-term use.[14] References 1. Pratt CH, King LE, Jr., Messenger AG, et al. Alopecia areata. Nat Rev Dis Primers 2017;3:17011. 2. Alkhalifah A. Alopecia areata update. Dermatol Clin 2013;31:93-108. 3. Wambier CG, King BA. Rethinking the classification of alopecia areata. J Am Acad Dermatol 2019;80:e45. 4. Aldhouse NVJ, Kitchen H, Knight S, 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;4:76. 5. Davey L, Clarke V, Jenkinson E. Living with alopecia areata: an online qualitative survey study. Br J Dermatol 2019;180:1377-1389. 6. FDA. The Voice of the Patient: Alopecia Areata. Public Meeting: September 11, 2017. Report Date: March 2018. Available at: https://www.fda.gov/files/about%20fda/published/Alopecia-Areata--The-Voice-of-the-Patient.pdf [Accessed 22 February 2022]. 7. Liu LY, King BA, Craiglow BG. Health-related quality of life (HRQoL) among patients with alopecia areata (AA): A systematic review. J Am Acad Dermatol 2016;75:806-812 e3. 8. Okhovat JP, Marks DH, Manatis-Lornell A, et al. Association Between Alopecia Areata, Anxiety, and Depression: A Systematic Review and Meta-analysis. J Am Acad Dermatol 2019.	

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		9. Macbeth AE, Holmes S, Harries M, et al. The associated burden of mental health conditions in alopecia areata: A population-based study in UK primary care. Br J Dermatol 2022. 10. Messenger AG, McKillop J, Farrant P, et al. British Association of Dermatologists' guidelines for the management of alopecia areata 2012. British Journal of Dermatology 2012;166:916-926. 11. Rossi A, Muscianese M, Piraccini BM, et al. Italian Guidelines in diagnosis and treatment of alopecia areata. G Ital Dermatol Venereol 2019;154:609-623. 12. Lyakhovitsky A, Aronovich A, Gilboa S, et al. Alopecia areata: a long-term follow-up study of 104 patients. J Eur Acad Dermatol Venereol 2019;33:1602-1609. 13. Muller SA, Winkelmann RK. Alopecia Areata. An Evaluation of 736 Patients. Arch Dermatol 1963;88:290-7. 14. Delamere FM, Sladden MM, Dobbins HM, et al. Interventions for alopecia areata. Cochrane Database Syst Rev 2008:Cd004413.	
The technology/ intervention	British Association of Dermatologists (endorsed by the Royal College of Physicians)	The basic description appears accurate.	Comment noted. No action required.
	Eli Lilly and Company	Lilly request that the wording be revised to: "It is a selective and reversible inhibitor of Janus kinase (JAK) 1 and JAK2."	Comments noted. The scope has been amended as suggested.
Population	British Association of Dermatologists	The population is appropriate, however, the current description of the adult population with severe disease does not include stipulation of duration of disease.	Comments noted. The scope has been kept broad to ensure that

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	(endorsed by the Royal College of Physicians)	The current trial data excluded those with disease of greater than 8 years. Any assessment of clinical efficacy should also include disease of longer duration, so that clinicians can stratify their patient population by those most likely to respond based on evidence. Also, it is possible that those with longer duration of disease may be older and therefore there may lead to indirect exclusion or discrimination of patients of an older age. It may also be worth considering children and young adults. Although the peak incidence of AA onset is those aged 25-29 years (Harries *et al.* https://onlinelibrary.wiley.com/doi/10.1111/bjd.20628), a significant proportion of patients first experience AA in childhood or adolescent years. This group tends to have a worse prognosis, and visible hair loss can have a profound impact psychologically at this stage of development.	NICE can evaluate the technology within its marketing authorisation. No action required.
	Eli Lilly and Company	The population in the draft scope has been defined appropriately.	Comment noted. No action required.
Comparators	British Association of Dermatologists (endorsed by the Royal College of Physicians)	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. Also, see “Questions for consultation” comments below.	Comments noted. The scope has been kept broad. The company will have the opportunity during the full evaluation to outline which comparators it considers to be most relevant. No action required.
	Eli Lilly and Company	Currently it is unclear what comprises ‘established clinical management’ of severe AA, as there are no therapies with marketing authorisations for this disease.	Comments noted. The scope has been kept broad. The company will have the opportunity

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		In practice a range of options may be trialled as off-label treatment for AA. Of these options, in the NHS there are limited centres which offer contact immunotherapy and often this therapy can be very burdensome. Other treatments that are sometimes tried are either only for short-term use, such as systemic corticosteroids, or as adjunctive therapy e.g., intralesional corticosteroids, minoxidil, methotrexate and other systemic treatments. A fuller discussion on the current treatment pathway is provided in response to the question for consultation further below. Importantly, as a result, 'established clinical management' may include no treatment.	during the full evaluation to outline which comparators it considers to be most relevant. No action required.
Outcomes	British Association of Dermatologists (endorsed by the Royal College of Physicians)	SALT Score – there is further detail needed: will this be an absolute reduction in SALT score or achievement of SALT50 (50% reduction in surface area affected, analogous to PASI50 in psoriasis)? Will an AA-specific quality of life tool or patient-reported outcome measures be considered? This is lacking from the current description. We are uncertain as to what the "Scalp Hair Assessment Score" is. The main hair loss sites to consider are scalp, eyebrows and eyelashes. However, beard hair loss should also be considered specifically (see "Equality" section below). Also, see "Questions for consultation" comments below.	Comments noted. The outcomes in the scope are broad and overarching. More specific outcomes relevant to these broader outcome headings can be considered as part of the evaluation process.
	Eli Lilly and Company	**<u>Clinical outcomes</u>** The key outcome measures presented relating to disease severity, improvement in hair loss, and adverse effects of treatment capture some of the most important health related benefits of baricitinib in alopecia areata (AA).	Comments noted. The company will have the opportunity during the full evaluation to present any issues related to modelling outcomes in this

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		Health-related quality of life The pivotal trials for baricitinib in AA collected EQ-5D-5L in line with the NICE reference case, as well as SF-36, the Hospital Anxiety and Depression Scale (HADS) and the disease-specific Skindex-16 for AA instrument. Importantly however, HRQoL outcomes in this indication are not expected to be adequately captured by the EQ-5D-5L instrument, with implications for the derivation of utility values for use the economic analysis. This arises because AA is characterised by non-scarring hair loss that, unlike other dermatological conditions, does not usually cause physical symptoms (beyond hair loss) or disability.[10, 15] The impact of AA on HRQoL is instead attributed to the significant psychological distress caused by hair loss.[1, 9, 16, 17] Owing to this mono-symptomatic aspect of AA, the five dimensions of health covered by the generic EQ-5D instrument, comprised of mobility, self-care, usual activities, pain/discomfort and anxiety/depression domains, do not adequately capture the dimensions of HRQoL that are affected by AA (in this case the psychological aspects), demonstrating a lack of content validity for the EQ-5D instrument in AA.[18, 19] Thus, even a post hoc responder analysis of EQ-5D may not differ significantly between responders and non-responders, despite the obvious health benefits that are gained due to hair regrowth in those that respond to baricitinib treatment.[20] Furthermore it is anticipated that this lack of content validity for EQ-5D will simultaneously result in a significant ceiling effect in the trial EQ-5D data, whereby many patients at baseline are likely to report almost “perfect health” on the EQ-5D instrument and therefore be unable to report an improvement from treatment in a responder analysis, despite entering the trial with severe AA (>50% scalp hair loss).Similar limitations have been reported from a recent trial funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme to treat Vitiligo.[21]	condition. No action required.

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		Mapping HRQoL data generated from HADS into EQ-5D-3L utility values, while offering a partial solution with respect to ceiling effects, is nonetheless likely to also underestimate the utility benefit of treatment response. This is because mapping these data into the EQ-5D instrument is likely to partially negate the increased sensitivity gained from the use of an instrument that is able to better quantify the HRQoL benefit of hair regrowth, due to the remaining lack of content validity of the EQ-5D instrument in AA. Therefore, despite the availability of a published mapping algorithm, the significant improvements observed HADS-measured outcomes during BRAVE-AA1 and BRAVE-AA2 do not fully translate into mapped EQ-5D utility data, even in responders.[20, 22] References 1. Pratt CH, King LE, Jr., Messenger AG, et al. Alopecia areata. Nat Rev Dis Primers 2017;3:17011. 9. Macbeth AE, Holmes S, Harries M, et al. The associated burden of mental health conditions in alopecia areata: A population-based study in UK primary care. Br J Dermatol 2022. 10. Messenger AG, McKillop J, Farrant P, et al. British Association of Dermatologists' guidelines for the management of alopecia areata 2012. British Journal of Dermatology 2012;166:916-926. 15. National Institute for Health and Care Excellence (NICE). Alopecia areata. Available at: https://cks.nice.org.uk/topics/alopecia-areata/. Last accessed: February 2022. 16. Rencz F, Gulácsi L, Péntek M, et al. Alopecia areata and health-related quality of life: a systematic review and meta-analysis. Br J Dermatol 2016;175:561-71. 17. Montgomery K, White C, Thompson A. A mixed methods survey of social anxiety, anxiety, depression and wig use in alopecia. BMJ Open 2017;7:e015468.	

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		18. Titeca G, Goudetsidis L, Francq B, Sampogna F, Gieler U, Tomas-Aragones L et al. The psychosocial burden of alopecia areata and androgenetica": A cross-sectional multicenter study among dermatological out-patients in 13 European Countries. *J Eur Acad Dermatol Venereol.* 2019; 34(2): 406-411. . 19. EuroQoL. 2018. Available from: https://euroqol.org/. Last accessed: Februrary 2022. 20. King B. Efficacy and safety of baricitinib in adults with alopecia areata: Phase 3 results from two randomized controlled trials (BRAVE-AA1 and BRAVE-AA2) FC02.05, EADV Congress 2021, 29 Sept–2 Oct. 21. Batchelor JM, Thomas KS, Akram P, et al. Home-based narrowband UVB, topical corticosteroid or combination for children and adults with vitiligo: HI-Light Vitiligo three-arm RCT. 2020;24:64. 22. Brazier J, Connell J, Papaioannou D, et al. A systematic review, psychometric analysis and qualitative assessment of generic preference-based measures of health in mental health populations and the estimation of mapping functions from widely used specific measures. Health Technol Assess 2014;18:vii-viii, xiii-xxv, 1-188.	
Economic analysis	British Association of Dermatologists (endorsed by the Royal College of Physicians)	Cost comparisons should also consider supportive treatments prescribed whilst someone is undergoing active treatment (i.e. wig provision) and potentially additional emotional support (e.g. psychologist or GP). Time off work and unemployment are higher in those with AA (Macbeth *et al.* https://onlinelibrary.wiley.com/doi/10.1111/bjd.21055). Can these wider social issues also be considered?	Comments noted. In line with NICE reference case, costs are considered from the NHS and Personal Social Services perspective. The committee, at its discretion, may request non-reference case analyses if appropriate. No action required.

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	Eli Lilly and Company	An economic analysis that addresses the requirements of the NICE reference case will be submitted. A lifetime time horizon will be implemented, and the NHS and PSS perspective will be used.	Comments noted. No action required.
Equality and Diversity	British Association of Dermatologists (endorsed by the Royal College of Physicians)	Having a disease duration cut-off of 8 years will indirectly lead to possible age-discrimination. 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 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 beard hair loss, where systemic medication is often required at an earlier stage. Would NICE also consider including adolescents (age 12-17) with severe AA? Treatment of children with AA is very challenging and increasing available treatments would have a significant impact in this patient population. 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.	Comments noted. These equality issues will be considered by the committee during the evaluation. No action required.

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	Eli Lilly and Company	None identified.	Comment noted. No action required.
Other considerations	British Association of Dermatologists (endorsed by the Royal College of Physicians)	Perhaps sub-groups based on location of hair loss location (see comment above on beard hair loss).	Comment noted. This subgroup has been added to the scope.
	Eli Lilly and Company	None	Comment noted. No action required.
Innovation	British Association of Dermatologists (endorsed by the Royal College of Physicians)	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. It is difficult to truly capture the impact of treatments for AA using QALYs, as this may not question the domains relevant to our patient population; perhaps another measure may need to be considered.	Comments noted. The evaluation committee will discuss the potentially innovative nature of this technology. No action required.
	Eli Lilly and	**'Step-change' in the management of AA**	Comments noted.

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	Company	The current management of AA relies on the off-label use of treatments that have not been well evaluated in clinical trials. Baricitinib is an oral medication which has a novel targeted mode of action involving the reversible inhibition of JAK1 and JAK2 enzymes and is expected to be the first licensed treatment for severe AA. The baricitinib clinical development programme for AA includes two robust global pivotal clinical trials to evaluate the safety and efficacy of baricitinib in a clinically homogeneous population of adult patients with severe AA defined as at least 50% scalp hair loss with current AA episode of more than 6 months' duration without spontaneous hair regrowth. Both studies were: • multicentre • randomised • double-blind • placebo-controlled • parallel-group • outpatient Baricitinib demonstrated key benefits across both pivotal Phase 3 trials, including consistent and clinically meaningful improvement across relevant signs and symptoms of AA. Appropriately for this chronic condition, the benefits were durable over 76 weeks of treatment. The demonstration of efficacy was performed in a refractory population of patients with chronic and extensive disease. Over half of all patients enrolled in the studies had a very severe AA at baseline as measured by Severity of Alopecia Tool (SALT 95 to 100 or 95% to 100% percentage of hair loss), with a mean duration of the current episode of 3.9 years. Approximately 90% of patients in the AA studies reported prior AA therapy, and over 50% had used	Innovation will be considered by the evaluation committee when formulating its recommendations. The company will have an opportunity to provide evidence on the innovative nature of its product in its submission. No action required.

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		systemic immunosuppressant or immunomodulator therapy. The integrated safety data from the AA clinical programme did not reveal new signals or safety concerns compared with the established safety profile. **<u>Benefits not captured in the QALY</u>** As described, changes in HRQoL in responders will not be fully captured by the EQ-5D-5L data collected in the trial due to its lack of content validity and the observed ceiling effects in patients with AA.[1, 16, 17] While disease-specific HRQoL measures such as HADS may better capture the impact of baricitinib-induced hair regrowth on HRQoL, as it has been demonstrated in BRAVE-AA1 and BRAVE-AA2, these changes are not anticipated to be fully translated into EQ-5D-3L utilities following the use of a mapping algorithm.[22] Therefore, neither mapping HADS into EQ-5D-3L nor EQ-5D-5L itself are likely to fully capture the health-related benefits associated with hair regrowth in those who respond to baricitinib treatment. Given these challenges with generating utility values that fully capture the value of treatment in this indication, HADS and disease-specific Skindex-16 AA HRQoL data generated during BRAVE-AA1 and BRAVE-AA2 may need to be considered qualitatively by the Committee alongside EQ-5D-based analyses, to better reflect the health related benefits of baricitinib in AA.[20] References 1. Pratt CH, King LE, Jr., Messenger AG, et al. Alopecia areata. Nat Rev Dis Primers 2017;3:17011. 16. Rencz F, Gulácsi L, Péntek M, et al. Alopecia areata and health-related quality of life: a systematic review and meta-analysis. Br J Dermatol 2016;175:561-71. 17. Montgomery K, White C, Thompson A. A mixed methods survey of	

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		social anxiety, anxiety, depression and wig use in alopecia. BMJ Open 2017;7:e015468. 20. King B. Efficacy and safety of baricitinib in adults with alopecia areata: Phase 3 results from two randomized controlled trials (BRAVE-AA1 and BRAVE-AA2) FC02.05, EADV Congress 2021, 29 Sept–2 Oct. 22. Brazier J, Connell J, Papaioannou D, et al. A systematic review, psychometric analysis and qualitative assessment of generic preference-based measures of health in mental health populations and the estimation of mapping functions from widely used specific measures. Health Technol Assess 2014;18:vii-viii, xiii-xxv, 1-188.	
Questions for consultation	British Association of Dermatologists (endorsed by the Royal College of Physicians)	**1. How is severity of AA determined in clinical practice?** This is generally done by the % extent of hair loss – usually using the Severity of Alopecia Tool (SALT) score. However, 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). **2. How is AA treated in clinical practice and by whom?** Primary care clinicians will treat many patients with mild disease with topical corticosteroids or observe those with limited disease. Secondary care dermatologists and paediatric dermatologists will treat the majority of individuals with severe disease, but referral rates are lower in those of lower socioeconomic status. There are also a limited number of tertiary care hair specialist dermatologists in the UK who will treat the full spectrum of extent of hair loss but will also be referred patients in whom there are complex issues or if available treatments have failed and specialist treatments are needed. Limiting the availability of the drug to those who have been reviewed by a tertiary specialist may lead to geographic inequalities in drug availability. Initiation of treatment varies. Current primary care guidance suggests that a “watch and wait” policy in recent-onset, limited patch AA is reasonable as spontaneous regrowth is common. When treatment is given in primary care	Comments noted. No action required.

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		this usually comprises a topical corticosteroid (see Harries *et al.* https://onlinelibrary.wiley.com/doi/10.1111/bjd.20628 for further information on issued prescriptions in this population). However, 1 in 5 people with limited disease will go on to develop extensive AA from which spontaneous regrowth, or response to treatment, is rare (Tosti *et al.* https://onlinelibrary.wiley.com/doi/10.1111/bjd.20628). Therefore, many hair specialists advocate earlier treatment to prevent progression to more extensive disease (Meah *et al.* https://pubmed.ncbi.nlm.nih.gov/32165196/). **3. Are treatments the same for the different types of AA, for example, alopecia totalis, alopecia universalis, alopecia areata incognita, alopecia areata ophiasis, alopecia areata sisaipho and alopecia barbae?** 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. **4. How and when is treatment effectiveness evaluated in clinical practice?** In clinical practice, patients are usually advised to wait for 6 months of a new treatment for AA before assessing for response (see consensus statements in Olsen *et al.* 2004 https://pubmed.ncbi.nlm.nih.gov/15337988/ and 2018 https://pubmed.ncbi.nlm.nih.gov/29128463/). Some therapies may take longer to see an effect, with data for both topical immunotherapy (Chiang *et al.* https://pubmed.ncbi.nlm.nih.gov/25128116/) and more recently baricitinib (King *et al.* https://pubmed.ncbi.nlm.nih.gov/34090959/) suggesting ongoing improvement even after this timeframe. Surface area regrowth, mainly by SALT score, but also ask what patients think. Sometimes, success for patients is different to success for clinicians – hair thickness, quality of hair, hair distribution are all factors. **5. Have all relevant comparators for baricitinib been included in the scope? Which treatments are considered to be established clinical**	

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		practice in the NHS for severe alopecia areata? See expert consensus paper (Meah *et al.* https://pubmed.ncbi.nlm.nih.gov/32165196/). In the NHS, most patients will have received a potent topical corticosteroid initially. After this, some may have had a course of oral corticosteroids; however, side effects limit longer treatment durations. Topical immunotherapy is only available in certain specialist centres (see British Hair and Nail Society website https://bhns.org.uk/), making access to this option challenging for many without significant travel requirements. Dithrocream has recently been taken off the market in the UK. Systemic immunosuppressants may be considered, with ciclosporin, methotrexate and mycophenolate mofetil being the main agents. However, side effects and maximum treatment duration (especially relevant for ciclosporin therapy, which is usually limited to 6-12 months' treatment) can impact on how long these therapies may be used. Evidence for efficacy is of poor quality. **6. Are the outcomes listed appropriate?** See comment above. **7. Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom baricitinib is expected to be more clinically effective and cost effective or other groups that should be examined separately?** See comments above. **8. Where do you consider baricitinib will fit in current treatment pathway?** There are no licensed treatment specific for AA. JAK inhibitors in general would fit at the stage when 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.	

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		topical contact immunotherapy can only treat *scalp* hair loss. **9. Do you consider baricitinib 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)?** Yes – 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). **10. Do you consider that the use of baricitinib can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** See comments above.	
	Eli Lilly and Company	**Q1) How is alopecia areata diagnosed in clinical practice?** AA is diagnosed by clinical history and physical examination. In case of diagnostic uncertainty, additional assessments such as trichoscopy, laboratory tests or a scalp biopsy can be used. **Q2) How is severity of alopecia areata determined in clinical practice?** Dermatologists will assess the extent of physical hair loss. The Severity of Alopecia Tool (SALT) score is the recommended tool to do this. Some dermatologists may combine this with a QoL measure, such as Dermatology Life Quality Index (DLQI) (modified to change questions about skin to be about scalp). In addition, given the psychological burden of AA, measures of anxiety and depression such as Patient Health Questionnaire (PHQ-9) and Generalized Anxiety Disorder (GAD-7) or HADS may be used. None of these	Comments noted. No action required.

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		QoL measure are specific to AA and therefore there is no consensus on which measures should be used. **Q3) How is alopecia areata treated in clinical practice and by whom?** First presentation will usually be to the GP who may initiate treatment for mild AA; treatment for severe AA would be initiated by a secondary care dermatologist following referral from the GP. Patients may not always be referred due to the belief that there are no further treatment options. Therapeutic algorithms for AA are generally based on the extent of hair loss (i.e. severity) and the patient's age.[10, 11] Topical and intralesional corticosteroids are the first-line treatments recommended for patients with limited patchy hair loss.[10, 11, 23] Supportive therapies like topical minoxidil are frequently proposed in clinical practice, but without a clear consensus on their usefulness.[10, 11, 23] Patients with severe disease are most often prescribed corticosteroids orally and/or topically using high-potency topical corticosteroids, but such treatment is necessarily time-limited. Other systemic agents are used after failure of oral corticosteroids or as corticosteroid-sparing agents to limit the adverse effects of prolonged corticotherapy.[23] Alternative options for severe disease are topical immunotherapy and phototherapy. Topical immunotherapy is not widely available, which limits its role in AA management. No consensus has been reached on the efficacy of phototherapy in AA, and, because of the serious side effects potentially associated with prolonged and repeated courses, this modality is not recommended.[1, 10, 11, 23] **Q4) Are treatments the same for the different types of alopecia areata, for example, alopecia totalis, alopecia universalis, alopecia areata incognita, alopecia areata ophiasis, alopecia areata sisaipho and alopecia barbae?**	

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		Treatment differs primarily based on severity of AA, but differences also arise due to the site of hair loss: • Localised scalp hair loss (i.e. mild AA): topical and intralesional steroids • Widespread hair loss including hair loss above ≥ 50% (i.e. severe AA; including AA totalis and AA universalis): contact immunotherapy (if available at a suitable centre), or systemic immunosuppressants • AA barbae (beard): this is a steroid sensitive site and prolonged super-potent steroids are not suitable; additionally, caution is required with injections • AA ophiasis: treated as severe AA, as this form of AA is known to be treatment-resistant • AA incognita (diffuse alopecia): treated as severe AA if unresponsive to topical minoxidil/clobetasol **Q5) How and when is treatment effectiveness evaluated in clinical practice?** This issue is not well defined in treatment guidelines; new treatments are typically initiated for a minimum 3-month trial, however clinical experts have suggested to Lilly that often 6 months are needed to evaluate response. Response is typically defined in terms of percentage hair loss or re-growth (e.g. using SALT score) but may additionally include physician global assessment, patient global assessment and DLQI. **Q6) Have all relevant comparators for baricitinib been included in the scope? Which treatments are considered to be established clinical practice in the NHS for severe alopecia areata?** Please refer to the answer to question 3 above. It should also be noted that there are no large randomised placebo controlled trials for existing	

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		established clinical management for AA in the UK. **Q7) Are the outcomes listed appropriate?** Please refer to our response to “Outcomes” in the decision problem section above. **Q8) Are the subgroups suggested in ‘other considerations appropriate? Are there any other subgroups of people in whom baricitinib is expected to be more clinically effective and cost effective or other groups that should be examined separately?** No other subgroups identified at this stage. **Q9) Where do you consider baricitinib will fit in current treatment pathway?** Lilly anticipates that baricitinib use would be as close to marketing authorisation as possible; baricitinib is anticipated to be indicated for the treatment of severe alopecia areata in adult patients defined as a Severity of Alopecia Tool (SALT) score ≥ 50 (that is, scalp hair loss of ≥50%). **Q10) Do you consider baricitinib 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)?** Yes. Please refer to our response to this question under “Innovation”, above. **Q11) Do you consider that the use of baricitinib can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?**	

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		Yes. Please refer to our response to this question under “Innovation”, above. **Q12) Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.** Data that will enable the Appraisal Committee to take account of these non-QALY benefits will all be derived from the pivotal phase III trials. **Q13) To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.** None identified. References 1. Pratt CH, King LE, Jr., Messenger AG, et al. Alopecia areata. Nat Rev Dis Primers 2017;3:17011. 10. Messenger AG, McKillop J, Farrant P, et al. British Association of Dermatologists’ guidelines for the management of alopecia areata 2012. British Journal of Dermatology 2012;166:916-926. 11. Rossi A, Muscianese M, Piraccini BM, et al. Italian Guidelines in diagnosis and treatment of alopecia areata. G Ital Dermatol Venereol 2019;154:609-623. 23. Meah N, Wall D, York K, et al. The Alopecia Areata Consensus of Experts (ACE) study: Results of an international expert opinion on treatments for alopecia areata. J Am Acad Dermatol 2020;83:123-130.	

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

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