National Institute for Health and Care Excellence

Health Technology Evaluation

Lebrikizumab for treating moderate to severe atopic dermatitis in people 12 years and over [ID4025]

Response to stakeholder organisation comments on the draft remit and draft scope

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Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Almirall (company)	Yes, this is appropriate for appraisal under the single technology appraisal evaluation route.	Comment noted, no action required.
	Sanofi (comparator)	no comment	Comment noted, no action required.
	British Association of Dermatologists (professional organisation)	Yes, it is appropriate	Comment noted, no action required.
	Eczema Outreach Support	Single tech appraisal is an appropriate evaluation route in our opinion.	Comment noted, no action required.

Section	Stakeholder	Comments [sic]	Action
	(patient organisation)		
	National Eczema Society (patient organisation)	Yes, it would be appropriate for NICE to evaluate this topic as a Single Technology Appraisal.	Comment noted, no action required.
Wording	Almirall (company)	Almirall is interested in putting forward a cost comparison case for lebrikizumab against dupilumab within lebrikizumab's intended marketing authorisation for treating moderate-to-severe atopic dermatitis (AD) in people 12 years and over. Please note that the positioning of lebrikizumab will be as a second line systemic treatment for moderate-to-severe AD (i.e. after the condition has not responded to at least 1 first line systemic treatment, or unsuitability for first line systemic treatment). This is the same positioning as dupilumab. Regarding the most appropriate treatment for lebrikizumab to cost compare against, we believe dupilumab to be the most appropriate. **Rationale for lebrikizumab cost comparison with dupilumab** Dupilumab is the most established and commonly used second-line systemic for the treatment of moderate-to-severe AD.	Comment noted. A cost comparison case can be made if a health technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication. However, NICE must evaluate products within their marketing authorisation. The comparators in this case have NICE guidance in place only for adults, hence the criteria for a cost comparison appraisal are not fully met.

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		Furthermore, our understanding is that due to safety concerns with janus kinase (JAK) inhibitors, many clinicians often consider biologics (predominantly dupilumab, but also tralokinumab) before JAK inhibitor use. Therefore, dupilumab is the most relevant comparator that lebrikizumab treatment would displace in clinical practice. Additionally, we would like to highlight that: 1. Lebrikizumab demonstrates comparable effectiveness at week 16 to dupilumab (and tralokinumab) according to early results from an Almirall network meta-analysis (NMA) 2. Lebrikizumab produces comparable durability of response to dupilumab (and tralokinumab) at week 52 3. Lebrikizumab's safety profile is comparable to other biologics for the treatment of moderate-to-severe AD. These 3 points will be expanded upon below. **Comparable effectiveness at week 16 to dupilumab (and tralokinumab) according to early results from an Almirall NMA** Almirall are currently conducting a NMA to evaluate the comparative efficacy between lebrikizumab and the biologics (dupilumab and tralokinumab). Almirall acknowledges that the assessment of treatment response based on a composite endpoint (EASI 50 combined	

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		with DLQI of at least 4) was considered the most relevant endpoint for decision making in NICE TA814. Indeed, the EAG used this composite outcome as the basis for assessing relative response, but also considered the EASI 75 outcome when data was not available for the composite outcome. As the composite endpoint findings for comparators (dupilumab and tralokinumab) are limited in availability or unpublished, it has not been possible for Almirall to conduct an NMA to include the composite endpoint as an outcome. However, early results from the NMA provide insights for key published endpoints from the clinical trials including EASI 50, EASI 75, EASI 90, IGA (0,1) + ≥2 point improvement from baseline. In summary, the early NMA combination therapy findings indicate that there is no statistically significant difference between lebrikizumab and other biological treatments (dupilumab and tralokinumab) with overlapping effects demonstrated. The monotherapy early NMA results again demonstrate non-inferiority to dupilumab and may indicate improved effects for lebrikizumab compared to tralokinumab. Please refer to the Addendum document provided which presents week 16 comparative efficacy results for lebrikizumab vs. dupilumab and tralokinumab in the treatment of adults and adolescents with moderate-to-severe AD. Results are available	

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		both for monotherapy treatment combination treatment (i.e. biologic treated in combination with topical corticosteroids). **2) Comparable durability of response to dupilumab (and tralokinumab) at week 52** Please refer to the Addendum document where we have presented data related to lebrikizumab's durability of response in the maintenance period of the ADvocate 1 and ADvocate 2 pivotal clinical trials. In summary, comparing independent trials for lebrikizumab, dupilumab and tralokinumab, suggests that lebrikizumab's effects are non-inferior to dupilumab and tralokinumab. Of interest, the proportion of patients completing week 0-16 of induction period treatment and then entering maintenance period is [redacted] compared to the proportions in the dupilumab and tralokinumab studies. **3) Safety profile is comparable to other biologics for the treatment of moderate-to-severe atopic dermatitis** In the pivotal trials, ADvocate 1 and ADvocate 2, the safety of lebrikizumab monotherapy compared with placebo was evaluated in adults and adolescents with moderate-to-severe AD. Most adverse events during the induction period were nonserious and mild or moderate in severity, including a low incidence (≤2.5%) of injection-site reactions in both of the	

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		ADvocate trials. The overall incidences of serious adverse events and trial discontinuations due to adverse events were low, however, conjunctivitis was more frequently reported in lebrikizumab-treated patients than in patients who received placebo.[i] A recently published integrated safety analysis in adolescent and adult patients with moderate-to-severe AD (based on eight lebrikizumab phase 2 and phase 3 clinical trials) found the frequency of patients reporting treatment emergent adverse events to be similar across trial treatment groups (Stein Gold et al., 2023). The safety profile in adults and adolescents was consistent with or without topical corticosteroid use. Consistent with the ADvocate trials, this integrated safety analysis highlighted conjunctivitis as the most common adverse event in lebrikizumab-treated patients. Ocular complications in AD can be related to either the underlying disease or therapeutic interventions, and the increased risk of developing conjunctivitis in adults with AD has been found to be significant and disease-severity-dependent. The association between AD and conjunctivitis is known and is observed in patients treated with other biologics, including dupilumab and tralokinumab. Indeed, this heightened awareness of conjunctivitis in AD (since revelation through real-world use of dupilumab) may bias recall within subsequent trials	

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		– including tralokinumab and lebrikizumab. However, it can be difficult to compare frequencies between lebrikizumab and other AD treatments due to different definitions used across study programmes for conjunctivitis clusters and varied patient populations.[ii] Of interest, there was a lower frequency of skin infections in lebrikizumab-treated patients compared with patients in the placebo group, with similar findings to other treatments for AD, including dupilumab[iii] and tralokinumab[iv], and could potentially be attributable to the restoration of cutaneous barrier function in patients with AD.	
	Sanofi (comparator)	no comment	No action required.
	Eczema Outreach Support (patient organisation)	No comments	No action required.
	National Eczema Society (patient organisation)	Yes, the wording of the remit reflects the issue(s) of clinical and cost effectiveness about this technology.	No action required.

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Timing issues	Alimirall (company)	Moderate-to-severe AD is an area of high unmet need, with more than half of patients currently under-treated and inadequately controlled[vvi], and the evaluation should be prioritised accordingly. Specifically, UK burden data has shown that 55% of moderate patients are uncontrolled and 77% of severe patients are uncontrolled. [vii]	Comment noted. NICE aims to publish guidance as soon as possible after the company receives the marketing authorisation and introduces the technology in the UK. NICE has scheduled this topic into its work programme.
	Sanofi (comparator)	no comment	No action required.
	British Association of Dermatologists (professional organisation)	Urgent for patients not benefitting from available treatments. In clinical practice we see patients who fail on dupilumab therapy responding to tralokinumab. It is likely that it would work the other way round. Therefore, a third, highly targeted biologic agent for atopic dermatitis (AD) would be welcome as it may further serve the heterogenous AD population. This is particularly important because highly targeted biologics are safer than JAK inhibitors for long-term therapy.	Comment noted. NICE aims to publish guidance as soon as possible after the company receives the marketing authorisation and introduces the technology in the UK. NICE has scheduled this topic into its work programme.
	Eczema Outreach Support (patient organisation)	We cannot comment on behalf of the NHS, however our patient group welcomes increased choice and treatment options for moderate to severe eczema in children 12+.	Comment noted, no action required.

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	National Eczema Society (patient organisation)	N/A	No action required.
Additional comments on the draft remit	National Eczema Society (patient organisation)	N/A	No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Alimirall (company)	The background is mostly accurate; however, we would draw your attention to the potential inaccuracy regarding tralokinumab as this is not currently recommended within NICE TA814 for use in young people aged 12–17. The technology section would benefit from inclusion of a summary description of lebrikizumab. Suggested text has been added to the bottom of this table in the “Any additional comments” box.	Comments noted. Since the publication of TA814, the marketing authorisation for tralokinumab has been extended to include people aged 12 to 17 years, and tralokinumab is commissioned by NHS England for this group. The background has been updated to state this. The scope is intended to provide a brief description of the technology, the condition

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		Of note, there is a minor typographic error at the end of “The technology” paragraph which should read “moderate” instead of “moderare”. Additionally, the disease background would benefit from inclusion of the high unmet need in people with moderate-to-severe disease whereby over half are currently under-treated and inadequately controlled.	and current treatment options. A detailed description of these aspects will be included in the company’s evidence submission and will be considered during the appraisal. The scope has been updated to correct the typographic error.
	Sanofi (comparator)	note: trials from 6months+ undergoing but no data read outs at present.	Comment noted. This has been updated to “It is being studied in ongoing phase III clinical trials”.
	British Association of Dermatologists (professional organisation)	The draft scope states that lebrikizumab has been studied in patients with moderate-to-severe AD, aged from 6 months to 18 years and over. While we are aware that clinical trials are ongoing going down to the lowest age range, this data is currently not published, or the trials are still ongoing.	Comment noted. This has been updated to “It is being studied in ongoing phase III clinical trials”.
	Eczema Outreach Support (patient organisation)	In this information topical therapies and guidance in relation to these are discussed, however they are outdated and here are inaccuracies. For example, Pimecrolimus is now licensed for use from age 3 months (Elidel 10 mg/g Cream - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk))	Comments noted. The background section has been updated to reflect that pimecrolimus is now licensed for use in people aged 3 months and over. The background section has been updated to remove “red”.

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		Atopic eczema is described as “red” in sentence two. This is not the case in all skin tones so should be removed. More information of the psycho-social impact of uncontrolled eczema is required. This impact is on patients and their families/carers. For example, adolescents miss school due to the condition and accessing treatments, they aren’t able to take part in regular “youth” activities because of potential flare-ups and experience sleepless nights. Carers can spend hours each day supporting their child to manage their skin including using topical treatments and attending hospital appointments. On top of this, the whole family deals with sleepless nights and the stress of the constant itching & scratching; the unpredictable flares are proven to increase the risk of anxiety and depression, especially in mothers. Over a quarter of parents caring for a child with moderate and severe eczema have missed time at work. Some cannot work at all. Parents/carers of children with eczema describe feelings of guilt, exhaustion, frustration and helplessness. Social life and relationships within the family can also be affected putting great strain on them.	The scope is intended to provide a brief description of the condition. NICE welcomes the input of patients and carers throughout the appraisal. Consultees will be invited to submit evidence and statements during the appraisal which will be considered by the committee.
	National Eczema Society	The background information appears to be accurate and complete.	Comment noted, no action required.

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	(patient organisation)		
Population	Alimirall (company)	Yes	Comment noted, no action required.
	Sanofi (comparator)	In line with previous AD TAGs suggestion to add 'candidates for systemic therapy'	Comment noted. The population has been updated.
	British Association of Dermatologists (professional organisation)	Yes	Comment noted, no action required.
	Eczema Outreach Support (patient organisation)	Need to define the age of the population in “The Technology” section; stating the minimum age is 12 and if there is a maximum age also.	Comment noted. The population has been updated.
	National Eczema Society (patient organisation)	Yes, the population is defined appropriately.	Comment noted, no action required.

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Subgroups	Almirall (company)	The subgroup “people for whom systemic therapies have been inadequately effective, not tolerated or contraindicated” will be explored using available lebrikizumab study data relevant to this subgroup that is available at the time of submission. In patients who have failed ciclosporin A or for whom ciclosporin A is not medically advisable, lebrikizumab 250 mg Q2W with concomitant topical corticosteroids significantly improved signs and symptoms and quality of life at week 16 in adults and adolescents with moderate-to-severe AD. Safety was consistent with the known profile of lebrikizumab.[viii] Regarding skin of colour, we do not presently have sufficient data to explore skin of colour as a separate subgroup since the majority of the patients in the ADvocate 1 and ADvocate 2 trials were White (approximately 68% in ADvocate 1 and 59% in ADvocate 2). Black and Asian patients comprised approximately 10% and 23% of the patients, respectively, across the two trials. In both ADvocate 1 & 2 trials, the proportions of Black and Asian participants are similar to and, in some instances, greater than those in other phase 3 trials of biologic agents for the treatment of atopic dermatitis. To further understand and characterise the safety and efficacy of lebrikizumab in diverse races and ethnic groups, two additional phase 3–3b trials are specifically analysing lebrikizumab therapy in patients with skin of colour (phase 3b trial; ClinicalTrials.gov number, NCT05372419) and Japanese patients (phase 3 trial; NCT04760314). [ix] The phase	Comments noted. The company is invited to include this information within its evidence submission. Skin colour has been excluded as a subgroup but the committee will consider whether any recommendations made could have a disproportionate effect on people with certain characteristics and whether any reasonable adjustments can be made to mitigate against this. The subgroup ‘people with atopic dermatitis affecting the hands’ has been removed from the scope.

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		3b lebrikizumab study has an estimated completion date of August 2024.[x] Regarding hand eczema, alitretinoin is a retinoid treatment approved for use in patients with severe chronic hand eczema that is unresponsive to potent topical corticosteroids. We do not intend to explore hand eczema as a separate subgroup in this appraisal. We assume that this subgroup was introduced with respect to the comparator alitretinoin. Hand eczema, while it may be a feature of atopic dermatitis, is considered a separate entity and alitretinoin is not licensed for the treatment of moderate-to-severe AD. Furthermore, evidence in the hand eczema subgroup was not considered in any previous moderate-to-severe AD NICE appraisals, despite inclusion in their respective scopes. We therefore consider that the hand eczema subgroup should be removed from the scope.	
	Sanofi (comparator)	Question regarding inclusion of HFE as this was not part of planned efficacy analysis. This would ensure consistency with other NICE TAGs in AD.	Comment noted. This subgroup has been removed from the scope.
	British Association of Dermatologists (professional organisation)	Treatment failure (covering all ages) on dupilumab, tralokinumab or JAK inhibitors, in addition to those who have failed conventional systemics. Patients aged 12-17 years.	Comments noted. If evidence allows the company can present subgroups in their submission for the committee to consider. Committee will consider the

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			relevance of these subgroups in line with NICEs methods outlined in the CHTE 2022 manual.
	Eczema Outreach Support (patient organisation)	Adolescents should be considered a specific subgroup, especially when considering the risks of poor treatment compliance. This will be especially important when assessing the feasibility of the treatment method and frequency.	Comments noted. If evidence allows the company can present subgroups in their submission for the committee to consider. Committee will consider the relevance of these subgroups in line with NICEs methods outlined in the CHTE 2022 manual.
	National Eczema Society (patient organisation)	We agree that the suggested subgroups are appropriate. We also suggest a subgroup of people with atopic dermatitis affecting the face. The ADvocate1, ADvocate2 and ADhere trials showed that lebrikizumab was effective in clearing and improving hand *and* facial eczema in most people with moderate to severe atopic eczema at week 16, both with and without concomitant topical steroid use. Facial eczema has a significant impact on patients' mental health as well as their physical health, as it affects such a visible area. If evidence allows, it would be helpful to patients with facial eczema if people with atopic dermatitis affecting the face was included as a subgroup.	Comment noted. If evidence allows the company can present subgroups in their submission for the committee to consider. Committee will consider the relevance of these subgroups in line with NICEs methods outlined in the CHTE 2022 manual.
Comparators	Almirall (company)	The comparators are mostly appropriate. However, please note that the positioning of lebrikizumab will be in line with other second line systemic biological treatments for moderate-to-	Comment noted. Lebrikizumab will be appraised within its marketing authorisation or a

Section	Consultee/ Commentator	Comments [sic]	Action
		severe AD (i.e. after the condition has not responded to at least 1 first line systemic treatment, or unsuitability for first line systemic treatment). As discussed in the subgroups section, alitretinoin is not licensed for the treatment of moderate-to-severe AD and we do not consider it to be a relevant comparator. This is consistent with the view taken by the EAGs of past NICE technology appraisals in this indication and its removal from the decision problem was undisputed by any the associated appraisal committees.	population for whom the company provides evidence if this is narrower than the marketing authorisation. Alitretinoin has been removed as a comparator.
	Sanofi (comparator)	No comment	Comment noted, no action required.
	British Association of Dermatologists (professional organisation)	Dupilumab will be main comparator, but the others listed in the draft scope are appropriate.	Comment noted, no action required.
	Eczema Outreach Support (patient organisation)	No comments	Comment noted, no action required.
	National Eczema	Yes, these are the standard treatments for moderate to severe atopic eczema currently used in the NHS with which the	Comment noted, no action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Society (patient organisation)	technology should be compared. Yes, all relevant comparators have been included.	
Outcomes	Almirall (company)	Yes, the majority of the outcomes are appropriate. However, during the NICE multiple technology appraisal (MTA), TA814, the EAG stated that clinical experts informed the EAG that the outcomes listed in the final scope issued by NICE of disease-free period, maintenance of remission, time to relapse and prevention of relapse are not terms that are commonly used in clinical practice in AD and are not defined for AD. Endpoints that could inform the duration of treatment response include: • Number of days free from TCS during treatment • Proportion of people maintaining for a set period of time the level of response (as defined in the study) initially achieved. Furthermore, during the scoping stage, the EAG noted that many studies were designed such that people responding to their initial allocated treatment entered a long-term follow-up phase that may or may not have included a control group, and frequently involved re-randomisation. Thus, comparative results for treatment versus comparator are not consistently available for the pre-specified outcome of the proportion of people maintaining, for a set period of time, the level of response (as defined in the study) initially achieved. As data are not available for most of the included studies, and comparative effectiveness across interventions of interest cannot be assessed, the EAG	Comments noted. The key outcomes relevant to the population are outlined in the scope but this is not an exhaustive list. The company is invited to include the outcomes commonly used in clinical practice in atopic dermatitis within its evidence submission. No action required.

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		decided not to report the limited details available for the outcome of maintenance of response and we would propose that the outcomes maintenance of remission, time to relapse and prevention of relapse are removed from the scope and replaced with the following outcomes consistent with the MTA. • Proportion of people who discontinue treatment (including those who discontinue treatment after a response at a set time point as defined in the study) • Proportion of people requiring use of rescue therapy during treatment • Number of days free from TCS during treatment.	
	Sanofi (comparator)	Given the chronic long-term nature of AD, the measure of symptom control should take into account sustained benefit over placebo preferably RCT over 52 weeks.	Comments noted. The company is invited to include this information within its evidence submission. All evidence and statements will be considered by the committee. No action required.
	British Association of Dermatologists (professional organisation)	Please refer to the Harmonising Outcome Measures for Eczema (HOME) initiative http://www.homeforeczema.org/. Long-term disease control/maintenance is now becoming an issue as some patients who have been largely or completely clear of their AD for several years after treatment with e.g. dupilumab. For how long they would need to continue; can effective treatments change the natural history and chronicity of	Comment noted. The company is invited to include this information within its evidence submission. All evidence and statements will be considered by the committee. No action required.

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		AD. The inclusion of some long-term outcomes would we welcomed.	
	Eczema Outreach Support (patient organisation)	The outcome measures included are all relevant however it will be important to specifically relate them to Harmonising Outcome Measures for Eczema (HOME) to ensure validity and reliability.	Comments noted. The key outcomes relevant to the population are outlined in the scope but this is not an exhaustive list. No action required.
	National Eczema Society (patient organisation)	Yes, these outcome measures will capture the most important health-related benefits (and harms) of lebrikizumab.	Comment noted. No action required.
Equality	Almirall (company)	Almirall is in agreement with the potential equality issues raised through previous technology evaluations for systemic treatments for moderate to severe atopic dermatitis (including MTA TA814): • The EASI might underestimate the severity of atopic dermatitis in people with brown or black skin • The DLQI may not account for anxiety and depression.	Comment noted. The committee will take into account skin colour and how this could affect the assessment of the severity of atopic dermatitis and response to treatment. The company is invited to submit evidence of any potential health-related benefits of lebrikizumab that may not be captured by measures such as the DLQI within its evidence submission.

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	Sanofi (comparator)	No comment	Comment noted, no action required.
	British Association of Dermatologists (professional organisation)	Appears to be appropriate	Comment noted, no action required.
	Eczema Outreach Support (patient organisation)	Consideration should be given to adolescents as a specific group as they may require higher levels of support and education to successfully manage their eczema. Consideration for patient groups living in rural areas or those on low incomes should be made if the treatment requires frequent hospital visits, particularly to central sites. Families may be unable to cover travel costs making the treatment inaccessible for them. Atopic eczema is described as “red” in sentence two of the *Background* paragraph. This is not the case in all skin tones so should be removed.	Comments noted. The experiences of all people with atopic dermatitis will be taken into account by the appraisal committee. The appraisal committee will consider the impact of its recommendations on people with protected characteristics as stated in equality legislation and according to its statutory duties for reducing health inequalities during the appraisal. No action needed. The background section has been updated to remove “red”.
	National Eczema Society	We do not think the proposed remit and scope require changing where equality is concerned	Comment noted, no action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	(patient organisation)		
Other considerations	Sanofi (comparator)	No comment	Comment noted, no action required.
	Eczema Outreach Support (patient organisation)	Update of current guidance in relation to first line treatments is needed.	Comments noted. No changes to the scope required.
	National Eczema Society (patient organisation)	N/A	Comment noted, no action required.
Questions for consultation	Alimirall (company)	**Q.** What is the impact of the safety update issued by the MHRA regarding JAK inhibitors on the treatment pathway for moderate to severe atopic dermatitis? **A.** Dupilumab is the most established and commonly used second-line systemic for the treatment of moderate-to-severe AD. The MHRA safety warning for JAK inhibitors applies to all chronic inflammatory conditions and this would therefore include AD.	Comments noted. The positioning of the technology in the treatment pathway will be considered by the committee during the appraisal. Comment noted. A cost comparison case can be made if a health technology is likely to provide similar or greater

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		Anecdotal feedback from clinicians informs us that most will always consider use of biologics before JAK inhibitors. **Q.** Is the technology likely to be similar in its clinical effectiveness and resource use to any of the comparators? Or in what way is it different to the comparators? **A.** As discussed above, a week 16 network meta-analysis is currently being undertaken and early results demonstrate similar clinical effectiveness/non-inferiority to the existing biologics dupilumab and tralokinumab, which lebrikizumab would displace in clinical practice. Of note, a key difference between lebrikizumab and the current biologics relates to [redacted] **Q.** Would it be appropriate to use the cost-comparison methodology for this topic? **A.** Yes, a cost comparison against dupilumab would be appropriate. **Q.** Is lebrikizumab likely to be used in combination with topical corticosteroids or as a monotherapy in clinical practice? **A.** The efficacy and safety of lebrikizumab has been evaluated through a robust clinical trial programme that includes both monotherapy and combination (with topical corticosteroid)	health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication. However, NICE must evaluate products within their marketing authorisation. The comparators in this case have NICE guidance in place only for adults, hence the criteria for a cost comparison appraisal are not fully met.

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		studies. The pivotal monotherapy studies (ADvocate 1 & ADvocate 2) best demonstrate the efficacy and safety of lebrikizumab from a methodological point of view without the bias / impact of topical corticosteroid therapy. However, we understand that biologics are more commonly used combination with topical corticosteroids and TCI as well as emollients in UK clinical practice.	
	Sanofi (comparator)	No comment	No action required.
	British Association of Dermatologists (professional organisation)	**Where do you consider lebrikizumab will fit into the existing care pathway for moderate to severe atopic dermatitis?** The same as for dupilumab, tralokinumab and JAK inhibitors, i.e. after inadequate response or failure of at least one conventional systemic treatment. **What is the impact of the safety update issued by the MHRA regarding JAK inhibitors on the treatment pathway for moderate to severe atopic dermatitis?** There has been no official change in the pathway. In practice, most dermatologists favour biologics first over JAK inhibitors due to better safety profile. However, there are specific situations where JAK inhibitors may be used first, e.g. coexistent alopecia areata. The new safety update will mean dermatologists consider the risks of JAK inhibitors very carefully, especially in	Comments noted. The positioning of the technology in the treatment pathway will be considered by the committee during the appraisal. The committee will consider uncaptured health benefits during the appraisal.

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		those with risk factors for cardiovascular disease, DVT/PE, malignancy, gastrointestinal disease and infection risk. **For a person needing systemic therapy to treat their atopic dermatitis would lebrikizumab be used as a first systemic treatment or after immunosuppressive therapies (such as ciclosporin, methotrexate, azathioprine)?** After one (England and Wales) or more (Scotland) systemic therapy, i.e. the same as dupilumab. When more safety data are available, this may need to be reviewed for earlier treatment with biologic therapy. More data on the effects of long-term treatment with biologics for AD is needed. **Is lebrikizumab likely to be used in combination with topical corticosteroids or as a monotherapy in clinical practice?** In combination with TCS, if needed. **Have all relevant comparators for lebrikizumab been included in the scope?** Yes, assuming that no data is yet available for newer biologic agents, e.g. nemolizumab. **Which treatments are considered to be established clinical practice in the NHS for moderate to severe atopic dermatitis in people aged 12 years and over? Do the treatments considered to be established clinical practice differ between people aged 12-17 and adults?**	

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		The treatment options stated in the background section are correct. In general, clinical practice is similar between people aged 12-17 yrs and adults, but there are some considerations, e.g. the recommended dosing is lower, despite young people often being of similar weight. Monitoring requirements (less so for biologics) mean that biologics can be more popular in young people (although some do not like the subcutaneous injections and therefore would prefer JAK inhibitors. **How should established clinical management be defined?** This is difficult, and the reason why we need a NICE guideline for managing AD in all ages. Previous health technology appraisals mean that the pathway for systemic treatment is defined to some extent. **Are the outcomes listed appropriate?** See above comments. **Are the subgroups suggested appropriate? Are there any other subgroups of people in whom lebrikizumab is expected to be more clinically effective and cost effective or other groups that should be examined separately?** See above comments. **Would lebrikizumab be a candidate for managed access?** Possibly.	

Section	Consultee/ Commentator	Comments [sic]	Action
		Do you consider that the use of lebrikizumab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? Yes, QALY is a blunt tool for measuring health-related benefits in skin disease. Experience from dupilumab is that this is a life-changing drug which among other things allows return to normal employment, family responsibilities, school, etc. These may be undercounted financial benefits. **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** There is limited data available. If possible, need to consider patient satisfaction, mental health benefits, improvement in sleep, patients' own time and costs, lost days from school/work, reduced hospital attendances, benefit on co-morbidities, e.g. asthma, rhinitis, alopecia areata. Employment data may be relevant, if available.	
	Eczema Outreach Support (patient organisation)	*Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.* Since this document was produced this doc was produced the following was published: Andrew Blauvelt et al, Efficacy and safety of lebrikizumab in moderate-to-severe atopic dermatitis: 52-week results of two randomized double-blinded placebo-controlled phase III	Comments noted. Committee will consider all evidence submitted as part of the appraisal during its decision-making process.

Section	Consultee/ Commentator	Comments [sic]	Action
		trials, *British Journal of Dermatology*, Volume 188, Issue 6, June 2023, Pages 740–748 *Which treatments are considered to be established in clinical practice in the NHS for moderate to severe atopic dermatitis in people aged 12 years and over? Do the treatments considered to be established clinical practice differ between people aged 12-17 and adults?* We know from our patient group that topical therapies, UV and immunosuppressive therapies differ which is why the guidelines for children, young people and adults should be updated and cannot be delayed.	
	National Eczema Society (patient organisation)	We understand that lebrikizumab is likely to be placed alongside the other biologic agents, dupilumab and tralokinumab, in the existing care pathway for moderate to severe atopic dermatitis. This would mean that patients would not be eligible for lebrikizumab before having tried at least one other systemic therapy (i.e. azathioprine, ciclosporin, methotrexate or mycophenelate mofetil). Since many patients have strong concerns about the serious potential side effects of the immunosuppressive therapies and alitretinoin, we consider that lebrikizumab should be offered as a first systemic treatment – particularly for patients with hand and/or facial atopic eczema. The side effects of lebrikizumab have tended to be non-serious, mild or moderate in severity in clinical trials.	Comment noted. NICE will appraise the technology within its marketing authorisation. The positioning of the technology in the treatment pathway will be considered by the committee during the appraisal. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		The safety update issued by the MHRA regarding JAK-inhibitors suggests that biologic agents such as lebrikizumab should come before JAK-inhibitors in the treatment pathway. We do not consider that the use of the technology would result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation.	
Additional comments on the draft scope	Alimirall (company)	The bottom of the "Economic analysis" section states that "The availability and cost of biosimilar and generic products should be taken into account." Please note that biosimilar and generic products do not relate to atopic dermatitis. "The technology" section would benefit from inclusion of a summary description of lebrikizumab. Suggested content: Lebrikizumab (Almirall Limited) is a humanised IgG4 monoclonal antibody that binds to IL-13 with a high affinity. Lebrikizumab-bound IL-13 can still bind to IL-13Rα1, but IL-4 receptor alpha (Rα)/IL-13Rα-1 heterodimerisation is inhibited, thereby blocking downstream signalling effects of IL-13. Lebrikizumab-bound IL-13 can also still bind IL-13Rα2 allowing internalisation and degradation of IL-13. It is administered by subcutaneous injection into the thigh or abdomen. Lebrikizumab does not currently have a marketing authorisation for treating people with	Comment noted. The availability and cost of biosimilar and generic products will only be taken into account if applicable for comparators. No action required. Comment noted. The scope is intended to provide a brief description of the technology. No changes to the scope required. A detailed description of these aspects will be included in the company's evidence submission and will be considered during the appraisal.

Section	Consultee/ Commentator	Comments [sic]	Action
		moderate-to-severe atopic dermatitis and who are candidates for systemic therapy. It has been studied in an extensive clinical trial programme that includes the following clinical trials: • As a monotherapy compared with placebo in people aged 12 and over with moderate to severe atopic dermatitis who are candidates for systemic therapy • In combination with topical corticosteroids compared with placebo in people aged 12 and over with moderate to severe atopic dermatitis who are candidates for systemic therapy • [study in progress] Combination therapy with topical corticosteroids in moderate to severe atopic dermatitis adult patients who have failed treatment with ciclosporin A or in whom ciclosporin A was not medically advised.	
	Sanofi (comparator)	No comment	No action required.
	Eczema Outreach Support (patient organisation)	Guidance on treating atopic eczema isn't up to date and needs to be reviewed	Comment noted. No changes to the scope required.
	National Eczema Society	N/A	No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	(patient organisation)		

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

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[i] Silverberg JI, et al. Two Phase 3 Trials of Lebrikizumab for Moderate-to-Severe Atopic Dermatitis. N Engl J Med. 2023 Mar 23;388(12):1080-1091. doi: 10.1056/NEJMoa2206714.
[ii] Stein Gold L, et al. Safety of Lebrikizumab in Adults and Adolescents with Moderate-to-Severe Atopic Dermatitis: An Integrated Analysis of Eight Clinical Trials. Am J Clin Dermatol. 2023 May 17:1–13. doi: 10.1007/s40257-023-00792-6.
[iii] Fleming P, Drucker AM. Risk of infection in patients with atopic dermatitis treated with dupilumab: a meta-analysis of randomized controlled trials. J Am Acad Dermatol. 2018;78:62–9.
[iv] Simpson EL, Merola JF, Silverberg JI, et al. Safety of tralokinumab in adult patients with moderate-to-severe atopic dermatitis: pooled analysis of five randomized, double-blind, placebo-controlled phase II and phase III trials. Br J Dermatol. 2022;187:888–99.
[v] Kleyn CE, Barbarot S, Reed C, et al. 2022. Burden of Moderate to Severe Atopic Dermatitis in Adults from France, Italy, and the UK: Patient-Reported Outcomes and Treatment Patterns. Dermatol Ther (Heidelb), 12, 1947-1965.
[vi] Halioua B, Corgibet F, Taieb C, et al. Therapeutic inertia in the management of patients with inadequately controlled atopic dermatitis. 31st EADV Congress, 2022 Milan, Italy.
[vii] Kleyn CE, Barbarot S, Reed C, et al. 2022. Burden of Moderate to Severe Atopic Dermatitis in Adults from France, Italy, and the UK: Patient-Reported Outcomes and Treatment Patterns. Dermatol Ther (Heidelb), 12, 1947-1965.
[viii] [Unpublished] Warren et al. Abstracts submitted to EADV 2023 conference.
[ix] Silverberg J et al. Letter to the Editor. Lebrikizumab for Moderate-to-Severe Atopic Dermatitis. N Engl J Med 388;24 nejm.org June 15, 2023; page 2292
[x] A Study of (LY3650150) Lebrikizumab to Assess the Safety and Efficacy of Adult and Adolescent Participants With Moderate-to-Severe Atopic Dermatitis and Skin of Color (ADmirable): https://clinicaltrials.gov/ct2/show/NCT05372419