National Institute for Health and Care Excellence

Single Technology Appraisal

Tralokinumab for treating moderate to severe atopic dermatitis

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	Leo Pharma	Yes it is both timely and appropriate to refer this topic to NICE for appraisal.	Comment noted.
	Sanofi	We agree this is an appropriate topic for NICE to appraise.	Comment noted.
	National Eczema Society	Yes, it would be appropriate to refer this topic to NICE for appraisal.	Comment noted.
Wording	Leo Pharma	Yes	Comment noted.
	Sanofi	No comment.	Comment noted.
	National Eczema Society	Yes, the wording of the remit reflects the issue(s) of clinical and cost effectiveness about this technology.	Comment noted.
Timing Issues	Leo Pharma	We would classify this as urgent based on the limited number of biologic treatments currently available for this patient group. Moderate to severe AD places a substantial economic burden on patients, caregivers, and payers. Generally healthcare resource utilization is higher in	Comment noted.

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		adults with AD than those without AD and resource utilization increases with worsening disease severity. In addition, having more therapeutic options that require minimal/no monitoring are likely to be particularly welcome in the current pandemic when in person hospital or GP attendance may be challenging.	
	Sanofi	No comment.	Comment noted.
	National Eczema Society	As tralokinumab is not yet licensed in the UK, a technology appraisal could be premature.	Comment noted. The Technology Appraisals process typically begins before marketing authorisation has been granted to allow recommendations to be issued as close to marketing authorisation as possible.
Additional comments on the draft remit	National Eczema Society	N/A	Noted.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Leo Pharma	For completeness, it should be made clear that ciclosporin is the only licensed oral systemic for Atopic Dermatitis.	Comment noted. The background section is only intended to give a

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			brief overview of the condition and the treatment pathway. Both licensed and off-license treatments are listed if they are part established care. The implications of having off-license comparators is anticipated to be discussed in the appraisal.
	Sanofi	No comment.	Noted.
	National Eczema Society	The background information appears to be accurate, although it is worth noting that tralokinumab failed in several large asthma trials (ATMOSPHERE program).	Comment noted. The background section is only intended to give a brief overview of the condition for which the technology is being appraised.
The technology/ intervention	Leo Pharma	Not fully- should be as follows: Tralokinumab is a fully human IgG4 monoclonal antibody that specifically binds to the type 2 cytokine interleukin-13 (IL-13) and inhibits its biological actions.	The technology section has been updated to Tralokinumab (brand name unknown, Leo Pharma UK) is an anti-interleukin (IL)-13 human immunoglobulin-G4 monoclonal antibody. It binds to the

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			type 2 cytokine interleukin-13 IL-13 inhibiting its action. It is administered by subcutaneous injection.
	Sanofi	No comment.	Noted
	National Eczema Society	Yes, as far as we are aware.	Comment noted.
Population	Leo Pharma	Yes, the population is defined appropriately Are the subgroups suggested in other considerations appropriate? Yes. The ECZTRA trial programme was not designed to test the local effect on the atopic dermatitis of tralokinumab on specific body areas, e.g. the hands and no specific hand eczema related outcomes were assessed. Although not assessed, it is likely that patients with hand eczema with the atopic dermatitis aetiology could benefit from treatment with tralokinumab. The subgroup “people for whom therapies have been inadequately effective, not tolerated or contraindicated” is relevant and should be clearly defined as “people for whom conventional systemic therapies have been inadequately effective, not tolerated or contraindicated”. Are there any other subgroups of people in whom tralokinumab is expected to be mode clinically effective and cost effective or other groups that should be examined separately? None currently aware of.	Comment noted. The potential subgroup “people for whom therapies have been inadequately effective not tolerated or contraindicated” has been updated to “people for whom systemic therapies have been inadequately effective not tolerated or contraindicated”. This is to make it clear that this

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			subgroup of people would be having second or later line systemic treatment for atopic dermatitis.
	Sanofi	No comment.	Comment noted.
	National Eczema Society	Yes, the population is defined appropriately. We do not think there are groups within this population that should be considered separately.	Comment noted.
Comparators	Leo Pharma	The comparator treatments listed in the scope document are used to treat patients with moderate to severe atopic dermatitis, however Phototherapy & oral steroids are not valid comparators for tralokinumab because these are short term treatment options and would not be used as chronic/long term/continuous treatment of AD. Alitretinoin is also not a valid comparator to tralokinumab based on its licenced indication and place in therapy in treatment of severe chronic hand eczema Alitretinion is used for hand eczema. Atopic dermatitis affecting the hands and chronic hand eczema are not synonymous (ref: https://www.nice.org.uk/guidance/ta534/documents/committee-papers page 79). The use of tralokinumab in UK is predicted to be in patients whose disease has not responded to at least one prior systemic therapy, (such as ciclosporin, methotrexate, azathioprine and mycophenolate mofetil), or where these are contraindicated or not tolerated. This would make the already approved biologic treatment, dupilumab the most relevant comparator.	Comments noted. The potential comparators listed in the scope represent systemic treatments used to treat moderate to severe atopic dermatitis in NHS clinical practice after topical corticosteroids or topical calcineurin inhibitors. These comparators are consistent with the scope for the ongoing appraisal of Baricitinib for treating moderate to severe atopic dermatitis (ID1622).

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		For patients with moderate to severe atopic dermatitis that are candidates for systemic therapy, systemic immunosuppressant agents are the established treatment. This includes the oral systemics of which ciclosporin is the only one licensed for atopic dermatitis, and more recently the biologic Dupilumab which is used in patients whose disease has not responded to at least one systemic therapy, (such as ciclosporin, methotrexate, azathioprine and mycophenolate mofetil), or these are contraindicated or not tolerated. Best supportive care could be defined as a combination of emollients, bathing products (e.g. aqueous cream , bath emollients, shower emollients), low-to-mid potency topical corticosteroids (TCS) and rescue therapy (higher potency topical or oral corticosteroids or topical calcineurin inhibitors [TCIs]). This is based on data from the ECZTRA trials and is supported by previous HTA submissions. Rates of usage assumed will be based on best available evidence.	The scope is inclusive of all potential relevant comparators and the appraisal committee will determine the most appropriate comparators for decision making. Tralokinumab will be appraised within its marketing authorisation or a population for whom the company provides evidence if this is narrower than the marketing authorisation Comments on best supportive care noted. Please note that since the consultation on this scope it is now expected that baricitinib will be an established treatment option by the time of the first

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			committee discussion of tralokinumab for treating atopic dermatitis. Baricitinib has therefore been added as a comparator to the scope.
	Sanofi	Established clinical practice in moderate to severe AD includes emollients, low to mid-potency topical corticosteroids (TCS), higher potency TCS or oral steroids as rescue therapy, topical calcineurin inhibitors, systemic immunosuppressants and dupilumab.	Comment noted. The scope is inclusive of all potential relevant comparators and the appraisal committee will determine the most appropriate comparators for decision making. Please note that since the consultation on this scope it is now expected that baricitinib will be an established treatment option by the time of the first committee discussion of

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			tralokinumab for treating atopic dermatitis. Baricitinib has therefore been added as a comparator to the scope.
	National Eczema Society	Yes, these are the standard treatments for moderate to severe atopic eczema currently used in the NHS with which the technology should be compared. As a fellow biologic agent, dupilumab could be described as 'best alternative care' to tralokinumab.	Comment noted. Please note that since the consultation on this scope it is now expected that baricitinib will be an established treatment option by the time of the first committee discussion of tralokinumab for treating atopic dermatitis. Baricitinib has therefore been added as a comparator to the scope.
Outcomes	Leo Pharma	Yes. Outcomes listed are appropriate.	Comment noted
	Sanofi	No comment.	Noted

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	National Eczema Society	Yes, these outcome measures will capture the most important health-related benefits (and harms) of tralokinumab.	Comment noted.
Economic analysis	Leo Pharma	The economic analysis for tralokinumab will be carried out based on the reference case guidance provided by NICE for the patients with moderate to severe atopic dermatitis that are candidates to systemic therapies and who have had insufficient response, intolerance or contraindication to at least one systemic therapy (CsA, MTX, azathioprine or mycophenolate mofetil). [redacted] Considering the chronic nature of atopic dermatitis, a lifetime time horizon will be implemented and analysed from an NHS perspective. [redacted]	Tralokinumab will be appraised within its marketing authorisation or a population for whom the company provides evidence if this is narrower than the marketing authorisation
	Sanofi	No comment.	Noted.
	National Eczema Society	N/A	Noted.
Equality and Diversity	Leo Pharma	N/A	Noted.
	Sanofi	We have found no issues relating to equity within the proposed scope.	Comment noted.
	National Eczema Society	We do not think the proposed remit and scope require changing.	Comment noted.
Other considerations	Leo Pharma	It is expected that tralokinumab will be used after unsatisfactory trial of at least one systemic immunosuppressant as defined by lack of response,	Tralokinumab will be appraised within its marketing authorisation

		intolerance or contraindication. Tralokinumab is expected to be used in the same place in the NICE treatment pathway as dupilumab. Would tralokinumab be used after dupilumab and vice versa? [redacted] Tralokinumab is expected to be placed in the same place in the NICE treatment pathway as dupilumab - as an alternative option. The decision about which biological therapy to initiate is one for the prescribing physician made in conjunction with the patient. Would a person who is a 'candidate for systemic therapy' already have had phototherapy? A candidate for systemic therapy has not necessarily tried phototherapy. The place of phototherapy in the therapeutic pathway for AD is not well defined, unlike psoriasis. Ease of access to phototherapy varies across the country. In addition, some clinicians do not consider a pulse therapy such as nbUVB an appropriate option for a chronic inflammatory condition such as AD. Patient factors such as skin phototype may also render patients unsuitable for phototherapy. Ref: Phototherapy for atopic dermatitis Clinics in Dermatology Volume 34, Issue 5, September–October 2016, Pages 607-613. Management of atopic dermatitis: safety and efficacy of phototherapy. Clin Cosmet Investig Dermatol. 2015; 8: 511–520.	or a population for whom the company provides evidence if this is narrower than the marketing authorisation Comments on treatment sequence noted. Comment noted.

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		Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I Journal of the European Academy of Dermatology and Venereology May 2018 Volume32, Issue5 page 657-82	
	Sanofi	Tralokinumab has previously been investigated for the treatment of severe asthma. If the marketing authorisation includes a cautionary statement regarding the use or discontinuation of tralokinumab in asthmatics, then we would consider this relevant to this appraisal.	Comment noted. The contraindications and cautions for tralokinumab stated in the Summary of Product Characteristics will be taken into account over the appraisal.
	National Eczema Society	We would like to see the ECZTRA trials published in a peer-reviewed journal before the proposed appraisal goes ahead.	Comment noted. NICE aims to issue technology appraisal guidance as close to the technology gaining its marketing authorisation and therefore the process generally starts before a technology has its license. NICE timings are independent of the company's publication

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			of its data in academic journals.
Innovation	Leo Pharma	Yes, we consider the technology to be innovative for the following reasons: - Novel drug, Tralokinumab is the first fully human monoclonal IL-13-antibody specifically targeting the IL13 cytokine, a key driver of atopic dermatitis. - Unlike conventional systemic immunosuppressants which require regular blood test monitoring, Tralokinumab, as a targeted therapy, does not require blood test monitoring, potentially reducing the number of hospital attendances, laboratory tests, time absent from work and attendant costs. [redacted] Whilst the introduction of Tralokinumab wouldn't necessarily lead to a 'step-change' in the management of eczema, nevertheless, its availability would broaden patient choice & help further embed the new practice of using biologics for long term management of the condition. This is vital given the limited existing treatment options for the condition, and will help increase the likelihood that people with moderate to severe eczema would find a treatment that is effective for them.	Comments noted.
	Sanofi	No comment.	Noted.
	National Eczema Society	The technology is being developed to treat moderate to severe eczema and as such is a rival to the existing drug dupilumab. It has a similar mode of action (dupilumab targets IL13 + IL4 receptors while tralokinumab targets IL13 only). However, we do consider the technology to have the potential to	Comments noted.

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		make a significant impact on health-related benefits and improve the way that current need is met, as Tralokinumab may work better for some patients. The introduction of tralokinumab would not necessarily lead to a 'step-change' in the management of eczema. Nevertheless, its availability would broaden patient choice, which is vital given the limited treatment options for the condition at present, and increase the likelihood that people with moderate to severe eczema would find a treatment that is effective for them. This is very important and necessary given the heterogeneous nature of eczema. People with moderate to severe eczema are currently faced with the choice of managing the best they can with topical treatments, in great pain and discomfort, or starting phototherapy (which is not universally available) or immunosuppressant drugs of uncertain efficacy with the potential for significant long-term harm through severe adverse side effects. For people who have tried and failed on at least one oral immunosuppressant drug, or who would not be eligible to take immunosuppressant drugs, dupilumab (at present the only biologic drug approved for atopic eczema) is the only option. Dupilumab, which has fewer potential side effects than immunosuppressant drugs, works by blocking both the IL-13 and IL-4 pathways. IL-13 and IL-4 are the two interleukins thought to contribute to atopic diseases. Tralokinumab works by binding specifically to IL-13, thereby preventing downstream IL-13 signalling. The relative contributions of IL-13 and IL-4 to atopic eczema development is unclear. Since people's eczema responds differently to the targeting of different pathways, tralokinumab is likely to work	

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		more effectively for some people than dupilumab. Dupilumab, while highly efficacious for many people, does not work effectively for everyone. Tralokinumab has undergone three Phase 3 trials (ECZTRA 1, 2 and 3), but we note that the results have not yet been published in a peer-reviewed journal. The following paragraphs should be read with this in mind. In the three Phase 3 trials, tralokinumab met its primary endpoints at week 16 as assessed by the Investigator Global Assessment score of clear or almost clear skin (IGA 0/1) and at least a 75% improvement in the Eczema Area and Severity Index score (EASI-75). It also demonstrated significant improvements in secondary endpoints at week 16 including extent and severity of skin lesions, itch and health-related quality of life measures. These improvements at week 16 were generally sustained. In ECZTRA 1 and 2, the majority of patients treated with tralokinumab 300 mg every two weeks who achieved a clinical response at week 16, maintained this response at week 52 without any use of topical steroids. ECZTRA 3 was a combination trial with topical steroids. In this trial, nine out of ten patients who achieved clear or almost clear skin with tralokinumab 300 mg in combination with topical steroids at week 16 maintained this response at week 32 when randomized to dosing every two weeks. Eight out of ten patients randomized to dosing every four weeks at week 16 maintained clear or almost clear skin at week 32, showing that going down to a lower dose – which would mean fewer hospital visits for patients – was not dissimilar to a higher dose in terms of results.	

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		The safety profile for tralokinumab was good. There was little meaningful difference in adverse event rates between tralokinumab and placebo. Adverse events that were higher for people on tralokinumab compared to placebo were upper respiratory tract infections and conjunctivitis. In ECZTRA 3, other adverse events included headache and injection site reactions. It appears that the risk of conjunctivitis, which is the most common side effect for dupilumab, may be lower with tralokinumab. We do not consider that the use of the technology would result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation.	

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Questions for consultation	Leo Pharma	Would it be appropriate to use the cost comparison methodology for this comparison [redacted] Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators? [redacted] Is the primary outcome that was measured in the trial or used to drive the model for the comparator still clinically relevant? The primary outcomes measured in the trials were EASI75 and IGA 0/1. However in clinical practice, EASI50 and a DLQI improvement of 4 points are now the main outcomes used following NICE guidance for Dupilumab. Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year? There is an ongoing trial (ECZTRA 7) where tralokinumab is being studied in a population of moderate to severe atopic dermatitis patients who have had lack of response, are intolerant or contraindicated to ciclosporin. This is a very relevant patient population and likely to be the patient population where tralokinumab will be used. [redacted]	Comment noted. It is anticipated that this technology will proceed as a single technology appraisal
	Sanofi	No comment	Noted.

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	National Eczema Society	N/A	Noted.
Additional comments on the draft scope	Sanofi	No comment.	Noted.
	National Eczema Society	N/A	Noted.

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