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HEALTH TECHNOLOGY BRIEFING
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Tralokinumab for atopic dermatitis

NIHRIO ID	10753	**NICE ID**	9983
Developer/Company	Leo Pharma UK	**UKPS ID**	650305

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Tralokinumab is in development for the treatment of moderate to severe atopic dermatitis (AD) uncontrolled with currently available therapies in adult patients who are candidates for systematic therapy. AD is a chronic inflammatory skin disease that affects both children and adults and is characterised by redness, itchiness, and scaling of the skin. Some people only have small patches of dry skin, but others may experience widespread red, inflamed skin all over the body. Patients with moderate to severe AD could come across with sleep disturbances, anxiety, depression, and poor quality of life. Currently, the management of AD involves the removal or treatment of trigger factors that contribute to the development of the disease.

Tralokinumab is a human monoclonal antibody that binds and neutralises the effect of the protein interleukin 13 (IL-13), which plays a key role in triggering immune system responses in patients leading to AD. Tralokinumab is taken subcutaneously (SC), and trial evidence suggests it has been associated with improvements in disease symptoms. If licensed, tralokinumab will offer an additional treatment option for adults with moderate to severe AD who are candidates for systematic therapy, who may or may not use steroid cream previously.

PROPOSED INDICATION

Treatment for adults with moderate to severe atopic dermatitis (AD) who are candidates for systematic therapy.[1,2,a]

TECHNOLOGY

DESCRIPTION

Tralokinumab is an anti-interleukin (IL)-13 human immunoglobulin-G4 monoclonal antibody that blocks the binding and signalling of IL-13 to its receptors.[3] Tralokinumab binds to the IL-13 cytokine at an epitope that overlaps with the binding site of the IL-13Rα receptors. This prevents IL-13 from binding to the IL-13Rα1 receptor and thus inhibits the subsequent downstream signaling.[4] By binding to and neutralising the effects of IL-13, tralokinumab results in an improvement of AD symptoms.[5]

Tralokinumab is in phase III clinical development for the treatment of severe AD uncontrolled with currently available therapies (ECZTRA 1 - NCT03131648[6]; ECZTEND - NCT03587805[7]; ECZTRA 2 - NCT03160885[2]; ECZTRA 3 - NCT03363854[1]; ECZTRA 7 - NCT03761537[8]). Tralokinumab dosing is a 600mg loading dose, followed by 300mg dosing every 2 weeks for 16 weeks, and maintenance dosing of 300mg every 2 weeks (with testing every 4 weeks from 16 to 52 weeks (in ECZTRA 1 and 2) and from 16 to 32 weeks in ECZTRA3).[b]

INNOVATION AND/OR ADVANTAGES

There is currently unmet treatment needs for some patients with moderate to severe AD, for whom management with topical glucocorticoids is not effective. Trial evidence suggests that combining tralokinumab treatment with topical glucocorticoids could demonstrate improvements in patients whose symptoms cannot be effectively controlled by topical glucocorticoids alone.[5] These technologies are widely used in AD treatments; however, they are associated with multiple systematic and topical side effects, precluding long-term use on a large body surface area.[5,9] Therefore, agents such as tralokinumab are needed as they reduce the need for high-dose topical glucocorticoids.[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Tralokinumab does not currently have a Marketing Authorisation in the EU/UK for any indication.

Tralokinumab is in phase II and phase III clinical development for a range of conditions including asthma, alopecia areata and ulcerative colitis.[10]

PATIENT GROUP

DISEASE BACKGROUND

AD also known as eczema or atopic eczema, is a chronic inflammatory skin disease characterised by erythema, pruritus, and scaling of skin that affects both children and adults.[11] AD has a complex and heterogeneous aetiology, characterised histologically by skin infiltration of inflammatory cells, predominantly lymphocytes, eosinophils, and mast cells.[12]

[a] Information provided by Leo Pharma UK on Pharmascan.
[b] Information provided by LEO Pharma.

Although the pathogenesis and aetiology of AD remain to be completely understood, this multifactorial disease likely results from complex crosstalk between genetic and environmental factors.[13,14] The symptoms of AD can have certain triggers, such as soaps, detergents, stress and the weather.[15] Exaggerated Th2-type response, disruption of the epidermal barrier functions, high level of serum IgE, and decreased production of antimicrobial peptides (AMPs) are the key findings in AD.[13,14]

Some people only have small patches of dry skin, but others may experience widespread red, inflamed skin all over the body. Although AD can affect any part of the body, it most often affects the hands, insides of the elbows, backs of the knees and the face and scalp in children.[15]

The appearance and location of AD changes with age. In infants it mainly affects the face and limb extensor surfaces. In adolescents and adults, it is most commonly localised and found on the flexural surfaces of the body, anterior and lateral neck, eyelids, forehead, scalp, face, wrists, dorsa of the feet, and hands.[11]

For patients with moderate to severe AD, skin lesions encompassing large surface areas are often associated with severe itching. These lesions can cause sleep disturbances and, in turn, symptoms of anxiety, depression, and poor quality of life.[16]

CLINICAL NEED AND BURDEN OF DISEASE

Although AD presents most frequently in childhood, it can present at any age.[17,18] Estimates vary due to the different population examined, but figures suggest that it affects about 10-30% of children and 2-10% of adults.[18-25] AD affects both males and females equally.[26]

It is indicated that AD affects 1 in 12 adults in the UK.[27] A 2016 international, cross-sectional, web-based survey estimated the prevalence of atopic dermatitis in several countries including the UK. Size of the sample population in the UK was 10,001. The prevalence of atopic dermatitis in this UK cohort was 2.5% (95% confidence interval [CI]: 2.2%, 2.8%). The prevalence was the same among males and females (2.5%). Depending on which scale was used for diagnosis, between 49-56% of cases were moderate, and 4-12% of cases were severe.[28]

According to the 2018-19 Hospital Episodes Statistics data, collectively there were 1,212 finished consultant episodes (FCE), 1,092 admissions which resulted in 542 day cases and 1,132 FCE bed days for other atopic dermatitis and atopic dermatitis unspecified (ICD-10 codes: L20.8 and L20.9) in England.[29]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Dermatitis has several causes, which may influence treatment. Management of dermatitis involves the removal or treatment of contributory factors that may trigger the development of the disease or worsen a flare. The management of AD also involve the use of different therapies to ease the symptoms.[15,30]

For the treatment of AD, NICE recommends a stepped approach. Treatment can be stepped up or down according to the severity of the condition and includes a range of therapies such as emollients, bandages, phototherapy topical and oral corticosteroids.[31]

CURRENT TREATMENT OPTIONS

The following treatment options have been recommended for moderate AD:[31]

- Emollients
- Moderate potency topical corticosteroids
- Topical calcineurin inhibitors (tacrolimus or pimecrolimus)
- Bandages
-

The following treatment options have been recommended for severe AD:[31]

- Emollients
- Potent topical corticosteroids
- Topical calcineurin inhibitors
- Bandages
- Phototherapy
- Oral corticosteroids

PLACE OF TECHNOLOGY

If licensed, tralokinumab will offer an additional treatment option for adults patients who have moderate to severe AD who are candidates for systematic therapy.

CLINICAL TRIAL INFORMATION

Trial	**ECZTRA 1, NCT03131648, EudraCT 2016-004200-65; adults aged 18 yrs and older who are candidates for systemic therapy; Tralokinumab versus placebo; phase III**
Sponsor	LEO Pharma
Status	Completed
Source of Information	Trial registry[6,32]
Location	EU (not UK), USA and Japan
Design	Randomised, parallel assignment, double blind, placebo-controlled
Participants	n=802; adults aged 18 yrs and older; diagnosis of AD as defined by the Hanifin and Rajka (1980) criteria for AD; diagnosis of AD for ≥1 yr; subjects who have a recent history of inadequate response to treatment with topical medications or for whom topical treatments are otherwise medically inadvisable; AD involvement of ≥10% body surface area at screening and baseline; subjects must have applied a stable dose of emollient twice daily (or more, as needed) for at least 14 days before randomisation.
Schedule[6,c]	**Experimental: Tralokinumab initial period -> Tralokinumab maintenance A**: Wk 0 to wk 16 - tralokinumab 600mg loading SC injection at day 0 - followed by tralokinumab 300mg SC injection regimen A (every 2 weeks) Wk 16 to wk 52 - tralokinumab 300mg maintenance SC injection regimen A (every 2 weeks) **Experimental: Tralokinumab initial period -> Tralokinumab maintenance B:**

[c] Information provided by LEO Pharma.

	Wk 0 to wk 16 – tralokinumab 600mg loading SC injection at day 0 - followed by 300mg tralokinumab SC injection regimen A (every 2 weeks) Wk 16 to wk 52 - tralokinumab 300mg maintenance SC injection regimen B (every 4 weeks) **Experimental: Tralokinumab initial period -> Placebo maintenance:** Wk 0 to wk 16 - tralokinumab 600mg loading SC injection at day 0 - followed by tralokinumab 300mg SC injection regimen A (every 2 weeks) Wk 16 to wk 52 - placebo maintenance SC injection regimen A (every 2 weeks) **Placebo Comparator: Placebo initial period -> Placebo maintenance:** Wk 0 to wk 16 - placebo loading SC injection at day 0 - followed by placebo SC injection regimen A (every 2 weeks) Wk 16 to wk 52 - placebo maintenance SC injection regimen A (every 2 weeks) **Experimental: Tralokinumab initial period -> Open-label tralokinumab:** Wk 0 to wk 16 - tralokinumab loading SC injection at day 0 - followed by tralokinumab SC injection regimen A (every 2 weeks) Wk 16 to wk 52 - tralokinumab maintenance SC injection regimen A (every 2 weeks) - open-label with allowed use of topical corticosteroids **Experimental: Placebo initial period -> Open-label tralokinumab:** Wk 0 to wk 16 - placebo loading SC injection at day 0 - followed by placebo SC injection regimen A (every 2 weeks) Wk 16 to wk 52 - tralokinumab maintenance SC injection regimen A (every 2 weeks) - open-label with allowed use of topical corticosteroids
Follow-up[d]	14 weeks, unless transferred to long-term extension (ECZTEND).
Primary Outcomes	Time frame: wk 0 to wk 16 • Subjects with Investigator's Global Assessment (IGA) score of 0 (clear) or 1 (almost clear) at wk 16. • Subjects achieving at least 75% reduction in Eczema Area and Severity Index [EASI].
Secondary Outcomes	Time frame: wk 0 to wk 16 • Change in Scoring Atopic Dermatitis (SCORAD) from baseline to wk 16. • Reduction of Worst Daily Pruritus numeric rating scale (weekly average) of at least 4 from baseline to week 16 • Change in Dermatology Life Quality Index (DLQI) score from baseline to week 16
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion data previously reported as October 2019.

Trial	**ECZTRA 2, NCT03160885, EudraCT 2016-004201-13; adults aged 18 yrs and older who are candidates for systemic therapy; Tralokinumab versus placebo; phase III**
Sponsor	LEO Pharma
Status	Completed

[d] Information provided by LEO Pharma.

Source of Information	Trial registry[2,33]
Location	EU (incl UK), USA, Canada and other countries
Design	Randomised, parallel assignment, double blinding, placebo-controlled
Participants	n=1028; adults aged 18 yrs and older; diagnosis of AD as defined by the Hanifin and Rajka (1980) criteria for AD; diagnosis of AD for ≥1 yr; subjects who have a recent history of inadequate response to treatment with topical medications or for whom topical treatments are otherwise medically inadvisable; AD involvement of ≥10% body surface area at screening and baseline; subjects must have applied a stable dose of emollient twice daily (or more, as needed) for at least 14 days before randomisation.
Schedule[2,e]	**Experimental: Tralokinumab initial period -> Tralokinumab maintenance A**: Wk 0 to wk 16 - tralokinumab 600mg loading SC injection at day 0 - followed by tralokinumab 300mg SC injection regimen A (every 2 weeks) Wk 16 to wk 52 - tralokinumab 300mg maintenance SC injection regimen A (every 2 weeks) **Experimental: Tralokinumab initial period -> Tralokinumab maintenance B:** Wk 0 to wk 16 – tralokinumab 600mg loading SC injection at day 0 - followed by 300mg tralokinumab SC injection regimen A (every 2 weeks) Wk 16 to wk 52 - tralokinumab 300mg maintenance SC injection regimen B (every 4 weeks) **Experimental: Tralokinumab initial period -> Placebo maintenance:** Wk 0 to wk 16 - tralokinumab 600mg loading SC injection at day 0 - followed by tralokinumab 300mg SC injection regimen A (every 2 weeks) Wk 16 to wk 52 - placebo maintenance SC injection regimen A (every 2 weeks) **Placebo Comparator: Placebo initial period -> Placebo maintenance:** Wk 0 to wk 16 - placebo loading SC injection at day 0 - followed by placebo SC injection regimen A (every 2 weeks) Wk 16 to wk 52 - placebo maintenance SC injection regimen A (every 2 weeks) **Experimental: Tralokinumab initial period -> Open-label tralokinumab:** Wk 0 to wk 16 - tralokinumab loading SC injection at day 0 - followed by tralokinumab SC injection regimen A (every 2 weeks) Wk 16 to wk 52 - tralokinumab maintenance SC injection regimen A (every 2 weeks) - open-label with allowed use of topical corticosteroids **Experimental: Placebo initial period -> Open-label tralokinumab:** Wk 0 to wk 16 - placebo loading SC injection at day 0 - followed by placebo SC injection regimen A (every 2 weeks) Wk 16 to wk 52 - tralokinumab maintenance SC injection regimen A (every 2 weeks) - open-label with allowed use of topical corticosteroids
Follow-up[e]	14 weeks, unless transferred to long-term extension (ECZTEND).
Primary Outcomes	Time frame: wk 0 to wk 16 • Subjects with Investigator's Global Assessment (IGA) score of 0 (clear) or 1 (almost clear) at wk 16. • Subjects achieving at least 75% reduction in Eczema Area and Severity Index [EASI].

[e] Information provided by LEO Pharma.

Secondary Outcomes	Time frame: wk 0 to wk 16 • Change in Scoring Atopic Dermatitis (SCORAD) from baseline to wk 16. • Reduction of Worst Daily Pruritus numeric rating scale (weekly average) of at least 4 from baseline to week 16 • Change in Dermatology Life Quality Index (DLQI) score from baseline to week 16
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion data previously reported as August 2019.

Trial	**ECZTRA 3, NCT03363854, EudraCT 2017-002065-21; adults aged 18 yrs and older who are candidates for systematic therapy; tralokinumab in combination with topical corticosteroids versus placebo in combination with corticosteroids; phase III**
Sponsor	LEO Pharma
Status	Completed
Source of Information	Trial registry[1,34]
Location	EU (incl UK), USA and Canada
Design	Randomised, parallel assignment (double masking), placebo-controlled
Participants	n=380; aged 18 yrs and above; diagnosis of AD as defined by the Hanifin and Rajka (1980) criteria for AD; history of AD for ≥1 yr; subjects who have a recent history of inadequate response to treatment with topical medications; AD involvement of ≥10% body surface area at screening and baseline; stable dose of emollient twice daily (or more, as needed) for at least 14 days before randomisation.
Schedule[1,f]	All arms in combination with topical corticosteroids **Experimental: Tralokinumab (initial) responders-> Tralokinumab (continuation A)** Wk 0 to 16 (initial period): Tralokinumab 600mg loading SC injection on day 0 followed by 300mg tralokinumab injection regimen A. (every 2 wks) Wk 16 to 32 (continuation period): Tralokinumab 300mg continuation SC injection regimen A. (every 2 wks) **Experimental: Tralokinumab (initial) responders-> Tralokinumab (continuation B)** Wk 0 to 16 (initial period): Tralokinumab 600mg loading SC injection on day 0 followed by 300mg tralokinumab injection regimen A. (every 2 wks) Wk 16 to 32 (continuation period): Tralokinumab 300mg continuation SC injection regimen B. (every 4 wks) **Experimental: Tralokinumab (initial) non-responders-> Tralokinumab (continuation A)** Wk 0 to 16 (initial period): Tralokinumab 600mg loading SC injection on day 0 followed by 300mg tralokinumab injection regimen A. (every 2 wks)

[f] Information provided by LEO Pharma.

	Wk 16 to 32 (continuation period): Tralokinumab 300mg continuation SC injection regimen A. (every 2 wks) **Experimental: Placebo (initial) non-responders-> Tralokinumab (continuation A)** Wk 0 to 16 (initial period): Placeboloading SC injection on day 0 followed by placebo injection regimen A. (every 2 wks) Wk 16 to 32 (continuation period): Tralokinumab 300mg continuation SC injection regimen A. (every 2 wks) **Placebo Comparator: Placebo (initial) responders-> Placebo (continuation A)** Wk 0 to 16 (initial period): Placebo loading SC injection on day 0 followed by placebo injection regimen A. (every 2 wks) Wk 16 to 32 (continuation period): Placebo continuation SC injection regimen A. (every 2 wks)
Follow-up[g]	14 weeks, unless transferred to long-term extension (ECZTEND)
Primary Outcomes	Time frame: wk 0 to wk 16 • Subjects with investigator's global assessment (IGA) score of 0 (clear) or 1 (almost clear) at wk 16 • Subjects achieving at least 75% reduction in Eczema Area and Severity Index (EASI).
Secondary Outcomes	Time frame: wk 0 to wk 16 • Change in scoring atopic dermatitis (SCORAD) from baseline to wk 16. • Reduction of worst daily pruritus numeric rating scale (NRS) (weekly average) of at least 4 from baseline to wk 16 • Change in dermatology life quality index (DLQI) score from baseline to wk 16.
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Actual primary completion date October 2018. Estimated study completion date September 2019.

Trial	**ECZTRA 7; NCT03761537; EudraCT 2018-000747-76; adults aged 18 yrs and older who are refractory or intolerant to cyclosporine; tralokinumab in combination with topical corticosteroids vs placebo in combination with topical corticosteroids; phase III**
Sponsor	LEO Pharma
Status	Ongoing
Source of Information	Trial registry[8,35]
Location	EU (incl UK)
Design	Randomised, parallel assignment, double blind, placebo-controlled
Participants	n=333 (planned); adults aged 18 yrs and over; diagnosis of AD as defined by the Hanifin and Rajka (1980) criteria for AD; history of AD for 1 year or more; subjects with a history within 1 year prior to screening of inadequate response

[g] Information provided by LEO Pharma.

	to treatment with topical medications or subjects for whom topical treatments are otherwise medically inadvisable AD involvement of 10% (or more) body surface area at screening and baseline (visit 3) according to component A of SCORAD; documented history of either no previous CSA exposure and not currently a candidate for CSA treatment OR previous exposure to CSA in which case CSA treatment should not be continued or restarted; subjects must have applied a stable dose of emollient twice daily (or more, as needed) for at least 14 days before randomisation.
Schedule[8,h]	Both arms in combination with topical corticosteroids **Experimental arm:** Tralokinumab 600mg loading SC injection on day 0 followed by 300mg tralokinumab injection every 2 wks **Placebo arm:** Placebo loading SC injection on day 0 followed by placebo SC injections every 2 wks
Follow-up[h]	14 weeks, unless transferred to long-term extension (ECZTEND)
Primary Outcomes	At least 75 reduction in EASI score (EASI75) [Time frame: wk 16]
Secondary Outcomes	• IGA score of 0 (clear) or 1 (almost clear) [Time frame: wk 0 to wk 16] • IGA score of 0 (clear) or 1 (almost clear) [Time frame: wk 0 to wk 26] • Change in SCORAD [Time frame: wk 0 to wk 16] • Change in SCORAD [Time frame: wk 0 to wk 26] • EASI75 response [Time frame: wk 26] • Reduction of worst daily pruritus NRS (weekly average) of at least 4 [Time frame: wk 16] • Reduction of worst daily pruritus NRS (weekly average) of at least 4 [Time frame: wk 26] • Change in DLQI score [Time frame: wk 0 to wk 16] • Change in DLQI score [Time frame: wk 0 to wk 26] • Adverse events [Time frame: wk 0 to wk 40] • Presence of anti-drug antibodies [Time frame: wk 0 to wk 40]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date November 2019 and estimated study completion date May 2020.

Trial	**ECZTEND, NCT03587805, EudraCT 2018-000746-19; adults aged 18 yrs and older who are candidates for systemic therapy ; tralokinumab; phase III extension**
Sponsor	LEO Pharma
Status	Ongoing
Source of Information	Trial registry[7,36]
Location	EU countries (incl UK), USA, Canada and Japan
Design	Single group assignment (open label)

[h] Information provided by LEO Pharma.

Participants	n=1125 (planned); adults aged 18 yrs and older; participants must have completed the treatment period(s) of one of the parent trials: LP0162-1325, -1326, -1339, -1341, -1342, or -1346.
Schedule[7,i]	Wk 0: SC injection of tralokinumab 600mg loading dose. From wk 2 up to wk 140*: SC injection of tralokinumab 150mg maintenance dose every 2 weeks * The length of treatment for each subject will depend on when they entered the trial.
Follow-up[i]	14 week follow up
Primary Outcomes	Number of adverse events from baseline through the last treatment visit (up to wk 142) [Time frame: from wk 0 up to wk 142]
Secondary Outcomes	• Investigator's global assessment (IGA) score of 0 (clear) or 1 (almost clear) at wks 16, 56, 80, 104, and 128 [Time frame: from week 16 up to week 128] • At least 75% reduction in eczema area and severity index (EASI75) relative to baseline in parent trial, at wks 16, 56, 80, 104, and 128 [Time frame: from wk 16 up to wk 128]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date June 2021. Estimated study completion date September 2021.

ESTIMATED COST

The cost of tralokinumab is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance. Tacrolimus and pimecrolimus for atopic eczema (TA82). August 2004.
- NICE technology appraisal guidance. Frequency of application of topical corticosteroids for atopic eczema (TA81). August 2004.
- NICE Technology Appraisal Guidance. Dupilumab for treating moderate to severe atopic dermatitis (TA534). August 2018.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Specialised Allergy Services (All ages). B09/S/b.
- NHS England. 2013/14 NHS Standard Contract for Specialised Dermatology Services (All ages). A12/S/a.

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OTHER GUIDANCE

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- Scottish Intercollegiate Guidelines Network (SIGN). Management of atopic eczema in primary care: A national clinical guideline (SIGN 125). March 2011.[39]
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ADDITIONAL INFORMATION

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