SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Adtralza 300 mg solution for injection in pre-filled pen

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tralokinumab is produced in mouse myeloma cells by recombinant DNA technology.

Each pre-filled pen contains 300 mg of tralokinumab in 2 ml solution (150 mg/ml).

Excipient with known effect

This medicinal product contains 0.2 mg of polysorbate 80 (E 433) in each pre-filled pen which is equivalent to 0.1 mg/ml.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection (injection)

Clear to opalescent, colourless to pale yellow solution, pH 5.5 and osmolarity approximately 280 mOsm/L.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adtralza is indicated for the treatment of moderate-to-severe atopic dermatitis in adult and adolescent patients 12 years and older who are candidates for systemic therapy.

4.2 Posology and method of administration

Treatment should be initiated by healthcare professionals experienced in the diagnosis and treatment of atopic dermatitis.

Posology

The recommended dose of tralokinumab for adult and adolescent patients 12 years and older is an initial dose of 600 mg administered as two 300 mg injections given by pre-filled pens.

This initial dose is followed by a 300 mg injection administered every other week as one 300 mg injection given by pre-filled pen.

At prescriber's discretion, every fourth week dosing may be considered for patients who achieve clear or almost clear skin after 16 weeks of treatment. The probability of maintaining clear or almost clear skin may be lower with every fourth week dosing (see section 5.1).

Consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment. Some patients with initial partial response may subsequently improve further with continued treatment every other week beyond 16 weeks.

Tralokinumab can be used with or without topical corticosteroids. The use of topical corticosteroids, when appropriate, may provide an additional effect to the overall efficacy of tralokinumab (see section 5.1). Topical calcineurin inhibitors may be used, but should be reserved for problem areas only, such as the face, neck, intertriginous and genital areas.

Missed dose

If a dose is missed, the dose should be administered as soon as possible. Thereafter, dosing should be resumed at the regular scheduled time.

Special populations

Elderly
No dose adjustment is recommended for elderly patients (see section 5.2). Limited data are available in patients > 75 years of age.

Renal impairment
No dose adjustment is needed in patients with renal impairment. Very limited data are available in patients with severe renal impairment (see section 5.2).

Hepatic impairment
No dose adjustment is needed in patients with hepatic impairment. Very limited data are available in patients with moderate or severe hepatic impairment (see section 5.2).

High body weight
For patients with high body weight (> 100 kg), who achieve clear or almost clear skin after 16 weeks of treatment, reducing the dose to every fourth week might not be appropriate (see section 5.2).

Paediatric population

The safety and efficacy of tralokinumab in children below the age of 12 years have not yet been established. No data are available.

Method of administration

For subcutaneous use.

The pre-filled pen should not be shaken. After removing the pre-filled pens from the refrigerator, they should be allowed to reach room temperature by waiting for 45 minutes before injecting the pre-filled pen.

Tralokinumab is administered by subcutaneous injection into the thigh or abdomen, except the 5 cm around the navel. If somebody else administers the injection, the upper arm can also be used.

For the initial 600 mg dose, two 300 mg pre-filled pens should be administered consecutively in different injection sites within the same body area.

It is recommended to rotate the injection site with each dose. Tralokinumab should not be injected into skin that is tender, damaged or has bruises or scars.

A patient may self-inject tralokinumab or the patient's caregiver may administer tralokinumab if their healthcare professional determines that this is appropriate. Proper training should be provided to patients and/or caregivers on the administration of tralokinumab prior to use. Detailed instructions for use are included at the end of the package leaflet.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity

If a systemic hypersensitivity reaction (immediate or delayed) occurs, administration of tralokinumab should be discontinued and appropriate therapy initiated.

Conjunctivitis

Patients treated with tralokinumab who develop conjunctivitis that does not resolve following standard treatment should undergo ophthalmological examination (see section 4.8).

Helminth infection

Patients with known helminth infections were excluded from participation in clinical studies. It is unknown if tralokinumab will influence the immune response against helminth infections by inhibiting IL-13 signalling.

Patients with pre-existing helminth infections should be treated before initiating treatment with tralokinumab. If patients become infected while receiving tralokinumab and do not respond to antihelminth treatment, treatment with tralokinumab should be discontinued until infection resolves.

Vaccinations

Live and live attenuated vaccines should not be given concurrently with tralokinumab as clinical safety and efficacy have not been established. Immune responses to the non-live tetanus and meningococcal vaccines were assessed (see section 4.5). It is recommended that patients should be brought up to date with live and live attenuated immunisations in agreement with current immunisation guidelines prior to treatment with tralokinumab.

Excipients

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per 150 mg dose, that is to say essentially “sodium-free”.

Adverse reactions to excipients

Adtralza contains polysorbate 80 (E 433) as an excipient, which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

The safety and efficacy of concurrent use of tralokinumab with live and live attenuated vaccines has not been studied.

Immune responses to non-live vaccines were assessed in a study in which adult patients with atopic dermatitis were treated with an initial dose of 600 mg (four 150 mg injections) followed by 300 mg every second (other) week administered as subcutaneous injection. After 12 weeks of tralokinumab administration, patients were vaccinated with a combined tetanus, diphtheria, and acellular pertussis vaccine, and a meningococcal vaccine and immune responses were assessed 4 weeks later. Antibody responses to both tetanus vaccine and meningococcal vaccine were similar in tralokinumab-treated and placebo-treated patients. No adverse interactions between either of the non-live vaccines or tralokinumab were noted in the study. Therefore, patients receiving tralokinumab may receive concurrent inactivated or non-live vaccinations.

For information on live and live attenuated vaccines, see section 4.4.

Interactions with cytochrome P450

Tralokinumab is not expected to undergo metabolism by hepatic enzymes or renal elimination. Clinically relevant interactions between tralokinumab and inhibitors, inducers, or substrates of metabolising enzymes are not expected, and no dose adjustment is needed.

The effects of tralokinumab on the pharmacokinetics (PK) of CYP substrates, caffeine (CYP1A2), warfarin (CYP2C9), metoprolol (CYP2D6), omeprazole (CYP2C19) and midazolam (CYP3A), were evaluated in atopic dermatitis patients after repeated administration. No effects were observed for caffeine and warfarin. Small numerical changes, which were not clinically significant, were observed for C_{max} of omeprazole, AUC of metoprolol and AUC and C_{max} of midazolam (the largest difference being for midazolam C_{max} with a decrease of 22%). Therefore, clinically relevant impact of tralokinumab on the pharmacokinetics of concomitant medicinal products metabolised by the CYP enzymes is not expected.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is limited amount of data from the use of tralokinumab in pregnant women.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).
As a precautionary measure, it is preferable to avoid the use of tralokinumab during pregnancy.

Breast-feeding

It is unknown whether tralokinumab is excreted in human milk or absorbed systemically after ingestion. A decision must be made whether to discontinue breast-feeding or to discontinue tralokinumab therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Animal studies did not show any effects on male and female reproductive organs and on sperm count, motility and morphology (see section 5.3).

4.7 Effects on ability to drive and use machines

Tralokinumab has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions are upper respiratory tract infections (23.4%; mainly reported as common cold), injection site reactions (7.2%), conjunctivitis (5.4%) and conjunctivitis allergic (2.0%).

Tabulated list of adverse reactions

Adverse reactions observed from clinical trials and post-marketing experience are presented in Table 1 by system organ class and frequency, using the following categories: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The frequencies are based on the initial treatment period of up to 16 weeks in the pool of 5 studies in the atopic dermatitis population.

Table 1: List of adverse reactions

MedDRA System Organ Class	**Frequency**	**Adverse reaction**
Infections and infestations	Very common Common	Upper respiratory tract infections Conjunctivitis
Blood and lymphatic system disorders	Common	Eosinophilia
Eye disorders	Common Uncommon	Conjunctivitis allergic Keratitis
General disorders and administration site conditions	Common	Injection site reactions

The long-term safety of tralokinumab was assessed in 2 monotherapy studies up to 52 weeks, and in a combination study with topical corticosteroids up to 32 weeks. The long-term safety of tralokinumab is further assessed in an open-label extension study (ECZTEND) for up to 5 years of treatment in adults and up to 2 years in adolescents 12 years and older with moderate-to-severe AD (atopic dermatitis) receiving 300 mg of tralokinumab every two weeks (Q2W). The long-term safety data were generally consistent with the safety profile observed up to week 16 in the pool of 5 adult studies.

Description of selected adverse reactions

Conjunctivitis and related events
Conjunctivitis occurred more frequently in atopic dermatitis patients who received tralokinumab (5.4%) compared to placebo (1.9%) in the initial treatment period of up to 16 weeks in the pool of 5 studies. Conjunctivitis was reported at a higher frequency in patients with severe atopic dermatitis compared to subjects with moderate atopic dermatitis in both the tralokinumab group (6.0 vs 3.3%; initial treatment period) and placebo group (2.2 vs 0.8%; initial treatment period). Most patients recovered or were recovering during the treatment period.

The rate of conjunctivitis in the initial 16 weeks treatment period was 22.0 events/100 patient years of exposure. The rate of conjunctivitis in the treatment period of the long-term open-label extension study (ECZTEND) was 2.93 events/100 patient years of exposure.

Keratitis was reported in 0.5% of subjects treated with tralokinumab during the initial treatment period. Of these, half were classified as keratoconjunctivitis, all were non-serious and mild or moderate in severity, and none led to treatment discontinuation.
The rate of keratitis in the initial 16 weeks treatment period was 1.7 events/100 patient years of exposure. The rate of keratitis in the treatment period of the long-term open-label extension study (ECZTEND) was 0.11 events/100 patient years of exposure.

Eosinophilia
Adverse reactions of eosinophilia were reported in 1.3% of patients treated with tralokinumab and 0.3% of patients treated with placebo during the initial treatment period of up to 16 weeks in the pool of 5 studies. Tralokinumab-treated patients had a greater mean initial increase from baseline in eosinophil count compared to patients treated with placebo. Eosinophilia (≥ 5 000 cells/mcL) was measured in 1.2% of tralokinumab-treated patients and 0.3% of placebo-treated patients in the initial treatment period. However, the increase in the tralokinumab-treated patients was transient, and mean eosinophil counts returned to baseline during continued treatment. The safety profile for subjects with eosinophilia was comparable to the safety profile for all subjects.

Eczema herpeticum
Eczema herpeticum was reported in 0.3% of the subjects treated with tralokinumab and in 1.5% of subjects in the placebo group in the initial treatment period of up to 16 weeks in the pool of 5 studies in atopic dermatitis. The rate of eczema herpeticum in the initial 16 weeks treatment period was 1.2 events/100 patient years of exposure. The rate of eczema herpeticum in the treatment period of the long-term open-label extension study (ECZTEND) was 0.67 events/100 patient years of exposure.

Immunogenicity
As with all therapeutic proteins, there is a potential for immunogenicity with tralokinumab.

Anti-drug-antibody (ADA) responses were not associated with any impact on tralokinumab exposure, safety, or efficacy in patients receiving tralokinumab for up to 6 years (in phase 2/phase 3 atopic dermatitis studies followed by the long-term extension study ECZTEND).
No immunogenicity-related adverse events such as immune-complex disease, serum sickness/serum sickness-like reactions, or anaphylaxis were observed.

In ECZTRA 1, ECZTRA 2, ECZTRA 3, and the vaccine-response study, the incidence of ADA up to 16 weeks was 1.4% in patients treated with tralokinumab and 1.3% in patients treated with placebo; neutralising antibodies were seen in 0.1% of patients treated with tralokinumab and 0.2% of patients treated with placebo.
The ADA incidence in patients who received tralokinumab up to 52 weeks was 4.6%; 0.9% had persistent ADA and 1.0% had neutralising antibodies.

ADA incidences in patients who received tralokinumab for up to 6 years (in phase 2/phase 3 atopic dermatitis studies followed by the long-term extension study ECZTEND) were similar to those observed after 52 weeks in ECZTRA 1 and 2.

Injection site reactions
Injection site reactions (including pain and redness) occurred more frequently in patients who received tralokinumab (7.2%) compared to placebo (3.0%) in the initial treatment period of up to 16 weeks in the pool of 5 studies. Across all treatment periods in the 5 studies in atopic dermatitis, the vast majority (99%) of injection site reactions were mild or moderate in severity, and few patients (< 1%) discontinued tralokinumab treatment. Most injections site reactions reported had a short duration with approximately 76% of the events resolving within 1 to 5 days.
The rate of injection site reactions in the initial 16 weeks treatment period was 51.5 events/100 patient years of exposure. The rate of injection site reactions in the treatment period of the long-term open-label extension study (ECZTEND) was 5.89 events/100 patient years of exposure.

Paediatric population

The safety of tralokinumab was assessed in patients 12 to 17 years of age (adolescents) with moderate-to-severe atopic dermatitis in a monotherapy study of 289 adolescents (ECZTRA 6) and in a long-term open-label extension study (ECZTEND) including 127 adolescents transferred from ECZTRA 6. The safety profile of tralokinumab in these patients followed through the initial treatment period of 16 weeks and maintenance treatment period of 52 weeks in ECZTRA 6, as well as in the long-term treatment period of up to 2 years in ECZTEND, was overall similar to the safety profile from studies in adults. In the initial treatment period of 16 weeks, however, conjunctivitis was reported at lower frequency with tralokinumab in adolescents (1.0% in ECZTRA 6) than in adults (5.4% in the pool of 5 studies), and, unlike in adults, the frequency of conjunctivitis allergic was similar for tralokinumab and placebo in adolescent patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is no specific treatment for tralokinumab overdose. In clinical studies with tralokinumab, single intravenous doses of up to 30 mg/kg and multiple subcutaneous doses of 600 mg every 2 weeks for 12 weeks were found to be well tolerated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other dermatological preparations, Agents for dermatitis, excluding corticosteroids, ATC code: D11AH07.

Mechanism of action

Tralokinumab is a fully human IgG4 monoclonal antibody that specifically binds to the type 2 cytokine interleukin-13 (IL-13) and inhibits its interaction with the IL-13 receptors. Tralokinumab neutralises the biological activity of IL-13 by blocking its interaction with the IL-13Rα1/IL-4Rα receptor complex. IL-13 is a major driver of human type 2 inflammatory disease, such as atopic dermatitis and inhibiting the IL-13 pathway with tralokinumab in patients decreases many of the mediators of type 2 inflammation.

Pharmacodynamic effects

In clinical trials, treatment with tralokinumab resulted in reduced levels of type 2 inflammation biomarkers in both lesional skin (CCL17, CCL18 and CCL26) and in blood (CCL17, periostin and IgE). In lesional skin, treatment with tralokinumab led also to reductions in epidermal thickness and to increase in marker of epithelial barrier integrity (loricrin). Skin colonisation with *Staphylococcus aureus* was reduced more than 10-fold in patients treated with tralokinumab. Treatment with tralokinumab also resulted in a shift of the stratum corneum lipid profile from a lesional to that of non-lesional skin, indicating improvement of the skin barrier integrity.

Immunogenicity

Anti-drug antibodies (ADA) were commonly detected. No evidence of ADA impact on pharmacokinetics, efficacy or safety was observed.

Clinical efficacy and safety

The efficacy and safety of tralokinumab as monotherapy and with concomitant topical corticosteroids (TCS) were evaluated in three pivotal randomised, double-blind, placebo-controlled studies (ECZTRA 1, ECZTRA 2 and ECZTRA 3) in 1 976 patients 18 years of age and older with moderate to severe atopic dermatitis defined by Investigator's Global Assessment (IGA) score of 3 or 4 (moderate or severe), an Eczema Area and Severity Index (EASI) score of ≥ 16 at baseline, and a minimum body surface area (BSA) involvement of ≥ 10%. Eligible patients enrolled into the three studies had previous inadequate response to topical medicinal products.

In all three studies, patients received 1) an initial dose of 600 mg tralokinumab (four 150 mg injections) on day 1, followed by 300 mg every two weeks (Q2W) up to week 16 or 2) matching placebo. In ECZTRA 3, patients received concomitant topical corticosteroids on active lesions as needed. Tralokinumab was administered by subcutaneous (SC) injection in all studies.

In ECZTRA 1 and ECZTRA 2, to evaluate the maintenance of response, patients responding to the initial 16-week treatment with tralokinumab (i.e. achieved IGA 0 or 1, or EASI-75) were re-randomised to 1) tralokinumab 300 mg Q2W or 2) tralokinumab 300 mg Q4W (alternating tralokinumab 300 mg and placebo Q2W) or 3) placebo Q2W up to 52 weeks. The main endpoints for evaluating maintenance of response were IGA 0 or 1 and EASI-75 at week 52. Patients responding to the

initial 16-week treatment with placebo continued on placebo. Subjects not achieving IGA 0 or 1 or EASI-75 at week 16 and subjects who did not maintain the response during the maintenance period were transferred to open-label treatment with tralokinumab 300 mg Q2W with optional use of topical corticosteroids. The studies had a treatment period of 52 weeks.

In ECZTRA 3, patients responding to the initial 16-week treatment with tralokinumab + TCS (i.e. achieved IGA 0 or 1, or EASI-75) were re-randomised to 1) tralokinumab 300 mg Q2W + TCS or 2) tralokinumab 300 mg Q4W + TCS (alternating tralokinumab 300 mg and placebo Q2W) up to 32 weeks. The main endpoints for evaluating maintenance of response were IGA 0 or 1 and EASI-75 at week 32. Patients responding to the initial 16-week treatment with placebo + TCS continued on placebo + TCS. Patients who at week 16 did not achieve IGA 0 or 1 or EASI-75 continued on tralokinumab 300 mg Q2W + TCS treatment, irrespectively of their initial treatment. The study had a treatment period of 32 weeks.

In ECZTRA 1, 802 patients were enrolled (199 to placebo, 603 to tralokinumab 300 mg Q2W).

In ECZTRA 2, 794 patients were enrolled (201 to placebo, 593 to tralokinumab 300 mg Q2W).

In ECZTRA 3, 380 patients were enrolled (127 to placebo + TCS, 253 to tralokinumab 300 mg Q2W + TCS).

Endpoints
In all three pivotal studies, the primary endpoints were achievement of IGA 0 or 1 (“clear” or “almost clear”) and a reduction of at least 75% in EASI (EASI-75) from baseline to week 16. Secondary endpoints included the reduction of itch as defined by at least a 4-point improvement in the Worst Daily Pruritus Numeric Rating Scale (NRS) from baseline to week 16, reduction in the SCORing Atopic Dermatitis (SCORAD) scale from baseline to week 16, and change from baseline to week 16 in the Dermatology Life Quality Index (DLQI). Additional secondary endpoints included reduction of at least 50% and 90% in EASI (EASI-50 and EASI-90, respectively) and reduction in Worst Daily Pruritus NRS (weekly average) from baseline to week 16. Other endpoints included change from baseline to week 16 in the Patient Oriented Eczema Measure (POEM), at least 4-point improvement in POEM, and Eczema-related Sleep NRS.

Baseline characteristics
In the monotherapy studies (ECZTRA 1 and ECZTRA 2), across all treatment groups, the mean age was 37.8 years, 5.0% of the patients were 65 years of age or older, the mean weight was 76.0 kg, 40.7% were female, 66.5% were White, 22.9% were Asian, and 7.5% were Black. In these studies, 49.9% of patients had a baseline IGA score of 3 (moderate atopic dermatitis, 49.7% of patients had a baseline IGA of 4 (severe atopic dermatitis), and 42.5% of patients had received prior systemic immunosuppressants (cyclosporine, methotrexate, azathioprine and mycophenolate). The mean baseline EASI score was 32.3, mean baseline Worst Daily Pruritus NRS was 7.8, mean baseline DLQI was 17.3, the baseline mean SCORAD score was 70.4, the baseline mean POEM score was 22.8, and the baseline mean physical and mental components of SF-36 were 43.4 and 44.3, respectively.

In the concomitant topical corticosteroids study (ECZTRA 3), across both treatment groups, the mean age was 39.1 years, 6.3% of the patients were 65 years of age or older, the mean weight was 79.4 kg, 45.0% were female, 75.8% were white, 10.8% were Asian, and 9.2% were black. In this study, 53.2% of patients had a baseline IGA score of 3, 46.3% of patients had a baseline IGA of 4, and 39.2 % of patients received prior systemic immunosuppressants. The baseline mean EASI score was 29.4, the baseline Worst Daily Pruritus NRS was 7.7, the baseline mean DLQI was 17.5, the baseline mean SCORAD score was 67.6, the baseline mean POEM score was 22.3.

Clinical response

Monotherapy studies (ECZTRA 1 and ECZTRA 2) – initial treatment period 0-16 weeks

In ECZTRA 1 and ECZTRA 2, from baseline to week 16, a significantly greater proportion of patients randomised to and dosed with tralokinumab achieved IGA 0 or 1, EASI-75, and/or an improvement of ≥ 4 points on the Worst Daily Pruritus NRS compared to placebo (see Table 2).

Table 2: Efficacy results of tralokinumab monotherapy at week 16 in ECZTRA 1 and ECZTRA 2 (FAS)

Monotherapy				
	ECZTRA 1		**ECZTRA 2**	
	Week 16		**Week 16**	
	Placebo	**Tralokinumab 300 mg Q2W**	**Placebo**	**Tralokinumab 300 mg Q2W**
Number of patients randomised and dosed (FAS)	197	601	201	591
IGA 0 or 1, % responders[a,b)]	7.1	15.8[#]	10.9	22.2[§]
EASI-50, % responders[a)]	21.3	41.6[§,e)]	20.4	49.9[§,e)]
EASI-75, % responders[a)]	12.7	25.0[§]	11.4	33.2[§]
SCORAD, LS mean change from baseline (± SE)[c)]	-17.2 (± 1.98)	-24.9[§] (± 1.23)	-13.8 (± 2.00)	-26.9[§] (± 1.06)
Pruritus NRS (≥ 4-point improvement, % responders)[a,d)]	10.3 (20/194)	20.0[#] (119/594)	9.5 (19/200)	25.0[§] (144/575)
DLQI, LS mean change from baseline (± SE)[c)]	-5.7 (± 0.63)	-7.5[#] (± 0.41)	-5.2 (± 0.68)	-8.6[§] (± 0.36)

LS=least squares; SE=standard error, FAS: Full Analysis Set - includes all patients randomised and dosed
If needed to control intolerable symptoms of atopic dermatitis, patients were permitted to receive rescue treatment at the discretion of the investigator.

a) Patients who received rescue treatment or had missing data were considered non-responders.
b) Responder was defined as a patient with IGA 0 or 1 (“clear“ or “almost clear” on a 0-4 IGA scale).
c) Data after initiation of rescue medication or permanent discontinuation of treatment were considered missing. Placebo based multiple imputation of missing data.
d) The percentage is calculated relative to the number of subjects with a baseline value ≥ 4.
e) Not adjusted for multiplicity.

*p<0.05, [#]p<0.01, [§]p<0.001

In both monotherapy studies (ECZTRA 1 and ECZTRA 2), tralokinumab reduced itch, as measured by the percent change from baseline in Worst Daily Pruritus NRS, already at Week 1 compared to placebo. The reduction in itch was observed in parallel with improvements in objective signs and symptoms of atopic dermatitis and quality of life.

In the two studies, fewer patients randomised to Adtralza 300 mg Q2W needed rescue treatment (topical corticosteroids, systemic corticosteroids, non-steroidal immunosuppressants) as compared to patients randomised to placebo (29.3% versus 45.3%, respectively, across both studies). Use of rescue treatment was higher if patients had severe atopic dermatitis at baseline (39.3% if under tralokinumab 300 mg Q2W treatment versus 56.7% in placebo group).

Monotherapy Studies (ECZTRA 1 and ECZTRA 2) – maintenance period (week 16-52)

To evaluate maintenance of response, 185 subjects from ECZTRA 1 and 227 subjects from ECZTRA 2 treated with tralokinumab 300 mg Q2W for 16 weeks who achieved IGA 0 or 1 or EASI-75 at week 16 were re-randomised to an additional 36-week treatment of 1) 300 mg tralokinumab every two weeks (Q2W) or 2) alternating tralokinumab 300 mg and placebo Q2W (tralokinumab Q4W) or 3) placebo Q2W, for a cumulative 52-week study treatment. Response rates (IGA 0/1 or EASI-75) at week 52 in the monotherapy pool were 56.2% and 50% for tralokinumab 300 mg Q2W and tralokinumab 300 mg Q4W among subjects achieving clinical response at week 16, respectively.

Table 3: Efficacy results (IGA 0 or 1 or EASI-75) at week 52 of subjects responding to tralokinumab 300 mg Q2W at week 16

	ECZTRA 1			**ECZTRA 2**		
	Treatment regimen Week 16-52[e)]			**Treatment regimen Week 16-52[e)]**		
Assessment at Week 52	**Tralokinumab 300 mg Q2W**	**Tralokinumab 300 mg Q4W**	**Placebo**	**Tralokinumab 300 mg Q2W**	**Tralokinumab 300 mg Q4W**	**Placebo**
IGA 0/1[a)] % responders [f)]	51.3[d)] (20/39)	38.9[d)] (14/36)	47.4 (9/19)	59.3[c)] (32/54)	44.9[d)] (22/49)	25.0 (7/28)
EASI-75[a)] % responders [g)]	59.6[d)] (28/47)	49.1[d)] (28/57)	33.3 (10/30)	55.8[b)] (43/77)	51.4[c)] (38/74)	21.4 (9/42)

If needed to control intolerable symptoms of atopic dermatitis, patients were permitted to receive rescue treatment at the discretion of the investigator.

a) Subjects who received rescue treatment or had missing data were treated as non-responders. The percentage is calculated relative to the number of subjects with response at week 16.

b) $p<0.001$ compared to placebo

c) $p<0.05$ compared to placebo

d) $p>0.05$ compared to placebo

e) All patients were initially treated with tralokinumab 300 mg Q2W week 0 to week 16.

f) IGA 0/1 at week 52 was evaluated in those subjects that had IGA 0/1 at week 16.

g) EASI-75 at week 52 was evaluated in those subjects that had EASI-75 at week 16.

Of the subjects randomised to tralokinumab, who did not achieve IGA 0 or 1 or EASI-75 at week 16 and were transferred to open-label tralokinumab 300 mg Q2W + optional TCS, 20.8% in ECZTRA 1 and 19.3% in ECZTRA 2 achieved IGA 0 or 1 at week 52, and 46.1% in ECZTRA 1 and 39.3% in ECZTRA 2 achieved EASI-75 at week 52. The clinical response was mainly driven by continued tralokinumab treatment rather than optional topical corticosteroids treatment.

32-Week concomitant TCS study (ECZTRA 3) – initial treatment period 0-16 weeks

In ECZTRA 3 from baseline to week 16, a significantly greater proportion of patients randomised to tralokinumab 300 mg Q2W + TCS achieved IGA 0 or 1, EASI-75, and/or an improvement of ≥ 4 points on the Worst Daily Pruritus NRS compared to placebo + TCS (see Table 4).

Table 4: Efficacy results of tralokinumab combination therapy with TCS at week 16 in ECZTRA 3 (FAS)

Combination therapy		
	ECZTRA 3	
	Week 16	
	Placebo + TCS	**Tralokinumab 300 mg Q2W + TCS**
Number of patients randomised and dosed (FAS)	126	252
IGA 0 or 1, % responders[a,b)]	26.2	38.9[*]
EASI-50, % responders[a)]	57.9	79.4[§, e)]
EASI-75, % responders[a)]	35.7	56.0[§]
SCORAD, LS mean change from baseline (± SE)[c)]	-26.7 (± 1.83)	-37.5[§] (± 1.27)
Pruritus NRS (≥ 4-point improvement, % responders)[a,d)]	34.1 (43/126)	45.4[*] (113/249)
DLQI, LS mean change from baseline (± SE)[c)]	-8.8 (± 0.57)	-11.6[§] (± 0.40)

LS=least squares; SE=standard error, FAS: Full Analysis Set - includes all patients randomised and dosed

If needed to control intolerable symptoms of atopic dermatitis, patients were permitted to receive rescue treatment at the discretion of the investigator. The supplied TCS did not constitute rescue medication.

a) Subjects who received rescue treatment or had missing data were treated as non-responders.
b) Responder was defined as a patient with IGA 0 or 1 (“clear“ or “almost clear” on a 0-4 IGA scale).
c) Data after initiation of rescue medication or permanent discontinuation of treatment were considered missing. Placebo based multiple imputation of missing data.
d) The percentage is calculated relative to the number of subjects with a baseline value ≥ 4.
e) Not adjusted for multiplicity.

*$p<0.05$, [#]$p<0.01$, [§]$p<0.001$.

In ECZTRA 3, subjects who received tralokinumab 300 mg Q2W from Week 0 to 16 used 50% less of the supplied topical corticosteroids at Week 16 as compared to subjects who received placebo.

In the concomitant TCS study (ECZTRA 3), tralokinumab + TCS reduced itch, as measured by the percent change from baseline in Worst Daily Pruritus NRS, already at Week 2 compared to placebo + TCS. The reduction in itch was observed in parallel with improvements in objective signs and symptoms of atopic dermatitis and quality of life.

32-Week concomitant TCS study (ECZTRA 3) – maintenance period 16-32 weeks

To evaluate maintenance of response, subjects treated with tralokinumab 300 mg + TCS for 16 weeks in the ECZTRA 3 study and who achieved IGA 0 or 1 or EASI-75 at week 16 were re-randomised to an additional 16-week treatment of 1) tralokinumab 300 mg every two weeks (Q2W) + TCS or 2) alternating tralokinumab 300 mg + TCS and placebo every two weeks (tralokinumab Q4W) for a cumulative 32-week study treatment. High maintenance of clinical efficacy at week 32 were seen across tralokinumab 300 mg Q2W + TCS and tralokinumab 300 mg Q4W + TCS among subjects achieving clinical response at week 16 (see Table 5).

Table 5: Efficacy results at week 32 of subjects achieving clinical response to tralokinumab 300 mg + TCS Q2W at week 16

	Tralokinumab 300 mg Q2W + TCS	**Tralokinumab 300 mg Q4W + TCS**
IGA 0/1 at week 32[a)] % responders[b)]	89.6 (43/48)	77.6 (38/49)
EASI-75 at week 32[a)] % responders[c)]	92.5 (62/67)	90.8 (59/65)

If needed to control intolerable symptoms of atopic dermatitis, patients were permitted to receive rescue treatment at the discretion of the investigator.

a) Subjects who received rescue treatment or had missing data were treated as non-responders. The percentage is calculated relative to the number of subjects with response at week 16.
b) IGA 0/1 at week 32 was evaluated in those subjects that had IGA 0/1 at week 16.
c) EASI-75 at week 32 was evaluated in those subjects that had EASI-75 at week 16.

Among all the subjects who achieved either IGA 0 or 1 or EASI-75 at week 16, the mean percentage improvement in EASI score from baseline was 93.5% at week 32 when maintained on tralokinumab 300 mg Q2W + TCS and 91.5% at week 32 for subjects on tralokinumab 300 mg Q4W + TCS.

Of the subjects randomised to tralokinumab 300 mg Q2W + TCS who did not achieve IGA 0 or 1 or EASI-75 at week 16, 30.5% achieved IGA 0/1 and 55.8% achieved EASI-75 at week 32 when treated continuously with tralokinumab 300 mg Q2W + TCS for additional 16 weeks.

The continued improvement among the subjects who did not achieve IGA 0 or 1 or EASI-75 at week 16 occurred in conjunction with the improvement of Worst Daily Pruritus NRS and objective signs of atopic dermatitis including SCORAD.

Table 6: Efficacy results of tralokinumab with concomitant TCS at weeks 16 and 32 in ECZTRA 3 in patients initially treated with tralokinumab Q2W + TCS

	Treatment regimen Week 16-32[d)]					
	Responders at Week 16[e)]				**Non-responders at Week 16**	
Patients randomised	**Q2W + TCS**		**Q4W + TCS**		**Q2W + TCS**	
	N=69		**N=69**		**N=95**	
Week number	**W16**	**W32**	**W16**	**W32**	**W16**	**W32**
EASI-50, % responders[a)]	100.0	98.6	97.1	91.3	63.2	76.8
EASI-90, % responders[a)]	58.0	72.5	60.9	63.8	1.1	34.7
EASI, LS % mean change from baseline (SE)[b)]	-90.5 (2.7)	-93.2 (2.3)	-89.3 (2.7)	-91.5 (2.3)	-46.9 (2.4)	-73.5 (2.0)
Pruritus NRS (≥ 4-point improvement, % responders)[a,c)]	63.2	70.6	64.2	61.2	27.4	38.9

LS: Least squares, SE: Standard error
If needed to control intolerable symptoms of atopic dermatitis, patients were permitted to receive rescue treatment at the discretion of the investigator.
a) Patients who received rescue treatment or had missing data were considered non-responders in the analyses.
b) Data after initiation of rescue medication or permanent discontinuation of treatment was excluded from the analyses.
c) The percentage is calculated relative to the number of subjects with a baseline value ≥ 4.
d) All patients were initially treated with tralokinumab 300 mg Q2W + TCS from week 0 to week 16. They were subsequently treated with tralokinumab 300 mg Q2W + TCS or Q4W + TCS.
e) Responders at week 16 are identified as patients achieving either IGA 0/1 and/or EASI-75.

Patient-reported outcomes

In both monotherapy studies (ECZTRA 1 and ECZTRA 2) and in the concomitant TCS study (ECZTRA 3) tralokinumab improved patient-reported symptoms of atopic dermatitis, as measured by POEM, and the impact of atopic dermatitis on sleep, as measured by Eczema-related sleep NRS, at week 16 compared to placebo. A higher proportion of patients treated with tralokinumab had clinically meaningful reductions in POEM, (defined as at least 4 point improvement) from baseline to week 16 compared to placebo.

Clinical efficacy and safety in adolescents

The efficacy and safety of tralokinumab monotherapy in adolescent patients was evaluated in a multicentre, randomised, double-blind, placebo-controlled study (ECZTRA 6) in 289 adolescent patients 12 to 17 years of age with moderate-to-severe atopic dermatitis defined by IGA score ≥ 3 in the overall assessment of atopic dermatitis lesions on a severity scale of 0 to 4, an EASI score ≥ 16 at baseline, and a minimum BSA involvement of ≥ 10%. Eligible patients enrolled into this study had previous inadequate response to topical medication.

Patients received an initial dose of 600 mg tralokinumab or 300 mg on day 1 followed by 300 mg Q2W or 150 mg Q2W, respectively, up to week 16. To evaluate the maintenance of response up to week 52, patients responding (i.e. achieved IGA 0 or 1, or EASI-75) to the initial 16-week treatment with tralokinumab 150 mg Q2W or 300 mg Q2W, without the use of rescue medication, were re-randomised to Q2W or Q4W (subjects initially treated with tralokinumab 300 mg were re-randomised 1:1 to tralokinumab 300 mg Q2W or tralokinumab 300 mg Q4W; subjects initially treated with tralokinumab 150 mg were re-randomised 1:1 to tralokinumab 150 mg Q2W or tralokinumab 150 mg Q4W). Patients not achieving IGA 0/1 or EASI-75 at week 16 and patients who did not maintain the response during the maintenance treatment period and those that used rescue medication during the initial period were transferred to open-label treatment with tralokinumab 300 mg Q2W with optional use of topical corticosteroids. Patients randomised to placebo in the initial treatment period who achieved a clinical response at week 16 continued to receive placebo Q2W in the maintenance treatment period.

In this study, the mean age was 14.6 years, the mean weight was 61.5 kg, 48.4% were female, 56.7% were White, 24.6% were Asian, and 11.1% were Black. At baseline 53.3% of patients had a baseline IGA score of 3 (moderate atopic dermatitis), 46.7% of patients had a baseline IGA of 4 (severe atopic dermatitis), the mean BSA involvement was 51.1%, and 21.1% of patients had received prior systemic immunosuppressants (cyclosporine, methotrexate, azathioprine and mycophenolate). Also, at baseline the mean EASI score was 31.7, the baseline Adolescent Worst Pruritus NRS score was 7.6, the baseline mean SCORAD score was 67.8, the baseline mean POEM score was 20.4, and the baseline mean Children Dermatology Life Quality Index (CDLQI) was 13.2. Overall, 84.4% of patients had at least one co-morbid allergic condition; 68.2% had allergic rhinitis, 50.9% had asthma, and 57.1% had food allergies. The primary endpoints were the proportion of patients with IGA 0 or 1 at week 16 (“clear” or “almost clear”) and the proportion of patients with EASI-75 (improvement of at least 75% in EASI from baseline) at week 16. Secondary endpoints included the reduction in itch, as measured by the proportion of subjects with ≥ 4 point improvement in Adolescent Worst Pruritus NRS from baseline, the absolute change in SCORAD from baseline to week 16 and the absolute change in CDLQI from baseline to week 16. Additional secondary endpoints included the proportion of subjects with EASI-50 and EASI-90. Other endpoints included proportion of patients with ≥ 6 point improvement in CDLQI and POEM at week 16.

Clinical response

The efficacy results at week 16 in the adolescent patients are presented in Table 7.

Table 7: Efficacy results of tralokinumab monotherapy in the adolescent patients at week 16 (FAS)

	ECZTRA 6		
	Placebo	**Tralokinumab 150 mg Q2W**	**Tralokinumab 300 mg Q2W**
Number of patients randomised and dosed (FAS)	94	98	97
IGA 0 or 1, % responders[a, b]	4.3	21.4[§]	17.5[#]
EASI-50, % responders[a]	13.8	45.9[e]	51.5[e]
EASI-75, % responders[a]	6.4	28.6[§]	27.8[§]
SCORAD, LS mean change	-9.7	-23.5[§]	-26.0[§]

from baseline (± SE)[c]	(±3.3)	(±2.7)	(±2.5)
Pruritus NRS ≥4-point improvement, % responders[a, d]	3.3 (3/90)	23.2[§] (22/95)	25.0[§] (24/96)
CDLQI, LS mean change from baseline (± SE)[c]	-3.8 (±0.9)	-5.5 (±0.7)	-6.2[#] (±0.7)

LS=Least squares; SE=Standard error; FAS=Full Analysis Set - includes all patients randomised and dosed
If needed to control intolerable symptoms of atopic dermatitis, patients were permitted to receive rescue treatment at the discretion of the investigator.

a) Patients who received rescue treatment from week 2 to week 16 or had missing data were considered non-responders

b) Responder was defined as a patient with IGA 0 or 1 ("clear" or "almost clear" on a 0-4 IGA scale).

c) Data after initiation of rescue medication or permanent discontinuation of treatment were considered missing. Placebo based multiple imputation of missing data.

d) The percentage is calculated relative to the number of subjects with a baseline value ≥ 4.

e) Not adjusted for multiplicity.

*$p<0.05$, [#]$p<0.01$, [§]$p<0.001$

A greater proportion of patients achieved EASI-90 at week 16 in the tralokinumab 150 mg group (19.4%) and tralokinumab 300 mg group (17.5%) compared with the placebo group (4.3%).

Greater improvements in patient-reported symptoms and impacts on quality of life (e.g., sleep) were observed at week 16 in the tralokinumab 150 mg and tralokinumab 300 mg groups compared with placebo, as measured by the proportion of patients with ≥ 6 point improvement in POEM and the proportion of patients with ≥ 6 point improvement in CDLQI.

In line with the monotherapy results in adults, adolescent efficacy data indicate that the clinical benefit achieved at Week 16 is sustained through Week 52.

Of the subjects randomised to tralokinumab who did not achieve IGA 0 or 1 or EASI-75 at week 16 or used rescue mediation during the initial period and were transferred to open label tralokinumab 300 mg Q2W + optional TCS, 33.3% achieved IGA 0 or 1 at week 52, and 57.8% achieved EASI-75 at week 52. The clinical response was mainly driven by continued tralokinumab treatment rather than the optional topical corticosteroids treatment.

Open-label extension study (ECZTEND)

The long-term efficacy of tralokinumab was further assessed in an open-label extension study (ECZTEND) in adults (1545 subjects) and in adolescents 12 years and older (127 subjects) with moderate-to-severe AD who had participated for up to 1 year in previous tralokinumab studies. For the total population, the median and maximum exposure time in ECZTEND was 2.6 and 5.1 years; for adolescent subjects, the median and maximum exposure time in ECZTEND was 1.8 and 2.2 years.

Efficacy data from ECZTEND indicate that the clinical benefit achieved during initial treatment and maintenance treatment is sustained during long-term treatment with 300 mg of tralokinumab every two weeks (Q2W) and optional TCS as needed.

Paediatric population

The licensing authority has deferred the obligation to submit the results of studies with tralokinumab in one or more subset of the paediatric population in atopic dermatitis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

After subcutaneous (SC) dose of tralokinumab median time to maximum concentration in serum (t_{max}) were 5-8 days. The absolute bioavailability of tralokinumab following SC dosing was estimated by population PK analysis to be 76%. In a phase 1 trial (10 subjects per arm), bioavailability was estimated to be 62% for the 150 mg dose and 60% for the 300 mg dose.

Steady-state concentrations were achieved by week 16 following a 600 mg starting dose and 300 mg every other week. Across clinical studies (ECZTRA 1, ECZTRA 2 and ECZTRA 3), the mean ±SD steady-state trough concentration ranged from 98.0±41.1 mcg/mL to 101.4±42.7 mcg/mL for 300 mg dose administered every other week.

Distribution

A volume of distribution for tralokinumab of approximately 4.2 L was estimated by population PK analysis.

Biotransformation

Specific metabolism studies were not conducted because tralokinumab is a protein. Tralokinumab is expected to degrade to small peptides and individual amino acids.

Elimination

Tralokinumab is eliminated through a non-saturable proteolytic pathway. Half-life is 22 days, consistent with the typical estimate for human IgG4 monoclonal antibodies targeting soluble cytokines. In ECZTRA 1, ECZTRA 2, and ECZTRA 3, clearance was estimated by population PK analysis to be 0.149 L/day. In phase 1 trials with intravenous dosing, clearance was estimated to be between 0.179 and 0.211 L/day

Linearity/non-linearity

Exposure of tralokinumab increases proportionally to the dose of tralokinumab between 150-600 mg.

Special populations

Gender

Gender was not found to be associated with any clinically meaningful impact on the systemic exposure of tralokinumab determined by population PK analysis.

Age
Age was not found to be associated with clinically relevant impact of systemic exposure of tralokinumab determined by population PK analysis. 109 subjects above 65 years were included in the analysis.

Race
Race was not found to be associated with any clinically meaningful impact on the systemic exposure of tralokinumab by population PK analysis.

Hepatic impairment
Tralokinumab, as a monoclonal antibody, is not expected to undergo significant hepatic elimination. No clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of tralokinumab. Mild hepatic impairment was not found to affect the PK of tralokinumab determined by population PK analysis. Very limited data are available in patients with moderate or severe hepatic impairment.

Renal impairment
Tralokinumab, as a monoclonal antibody, is not expected to undergo significant renal elimination. No clinical studies have been conducted to evaluate the effect of renal impairment on the pharmacokinetics of tralokinumab. Population PK analysis did not identify mild or moderate renal impairment as having a clinically meaningful influence on the systemic exposure of tralokinumab. Very limited data are available in patients with severe renal impairment.

High body weight
Tralokinumab exposure (AUC) was lower in subjects with higher body weight (see section 4.2).

Table 8: Area under the curve (AUC) by weight

Weight (kg)	75	100	120	140
AUC (mcg*day/mL)	1532	1192	1017	889
Ratio AUC 75 kg	1	0.78	0.66	0.57

Calculated AUC at steady-state for the dosing interval for 300 mg Q2W for a subject of a certain weight based on the relation between Clearance and weight.
Clearance = $0.149 \times (W/75)^{0.873}$. AUC = F × Dose Clearance, where F = 0.761.

Paediatric population
The pharmacokinetics of tralokinumab in paediatric patients below 12 years has not yet been studied.
For adolescents 12 to 17 years of age with atopic dermatitis, the mean ±SD steady-state through concentration (at week 16) was 112.8±39.2 mcg/mL for 300 mg dose administered every other week.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity (including safety pharmacology endpoints) and toxicity to reproduction and development.

The mutagenic potential of tralokinumab has not been evaluated; however monoclonal antibodies are not expected to alter DNA or chromosomes.

Carcinogenicity studies have not been conducted with tralokinumab. An evaluation of the available evidence related to IL-13 inhibition and animal toxicology data with tralokinumab does not suggest an increased carcinogenic potential for tralokinumab.

Enhanced pre- and postnatal studies with tralokinumab in monkeys did not identify adverse effects in maternal animals or their offspring up to 6 months post-partum.

No effects on fertility parameters such as reproductive organs, menstrual cycle and sperm analysis were observed in sexually mature monkeys treated subcutaneously with tralokinumab up to 350 mg/animal (females) or 600 mg/animal (males) (AUC exposure up to 15-fold higher than in human patients receiving tralokinumab 300 mg every 2 weeks).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate trihydrate (E 262)
Acetic acid (E 260)
Sodium chloride
Polysorbate 80 (E 433)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

If necessary, pre-filled pens may be kept at room temperature in the original carton up to 30 °C for a maximum of 14 days, within their shelf-life, without being refrigerated again during this period. Do not store above 30 °C. If the carton needs to be removed permanently from refrigerator, the date of removal may be recorded on the carton. After removal from the refrigerator, Adtralza must be used within 14 days or discarded.

6.4 Special precautions for storage

Store in a refrigerator (2 °C-8 °C).
Do not freeze.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

2 ml solution in a siliconised type-1 clear glass syringe in a pre-filled pen, with a 27 gauge ½ inch, thin wall stainless steel staked needle.

Pack size:
- 2 pre-filled pens
- Multipack containing 6 (3 packs of 2) pre-filled pens

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The solution should be clear to opalescent, colourless to pale yellow. If the solution is cloudy, discoloured or contains visible particulate matter, the solution should not be used. Do not use if the pre-filled pen is damaged or has been dropped on a hard surface.

After removing the pre-filled pen from the refrigerator, it should be allowed to reach room temperature by waiting for 45 minutes before injecting the pre-filled pen.

Adtralza contains a sterile solution for injection. Discard any unused product remaining in the pre-filled pen.

7 MARKETING AUTHORISATION HOLDER

LEO Pharma A/S
Industriparken 55
DK-2750 Ballerup
Denmark

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