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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

ADTRALZA

International non-proprietary name: tralokinumab

Pharmaceutical form: solution for injection in pre-filled syringe

Dosage strength(s): 150 mg

Route(s) of administration: subcutaneous

Marketing Authorisation Holder: Leo Pharmaceutical Products Sarath

Marketing Authorisation No.: 68229

Decision and Decision date: approved on 24 February 2022

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.

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1 Terms, Definitions, Abbreviations

AD	Atopic dermatitis
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC _{0-24h}	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C _{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
Da	Dalton
DDI	Drug-drug interaction
EASI	Eczema Area and Severity Index
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
FDA	U.S. Food and Drug Administration
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC ₅₀	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
IGA	Investigator's Global Assessment
IL	Interleukin
INN	International nonproprietary name
ITT	Intention-to-treat
IV	Intravenous
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric Study Plan (US-FDA)
RMP	Risk Management Plan
SC	Subcutaneous
SAE	Serious adverse event
SCORAD	Scoring Atopic Dermatitis
SwissPAR	Swiss Public Assessment Report
TCS	Topical corticosteroids
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status

The applicant requested the status of a new active entity for the active substance tralokinumab of the medicinal product mentioned above.

2.2 Indication and Dosage

2.2.1 Requested Indication

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

2.2.2 Approved Indication

Adtralza is indicated for the treatment of adult patients with moderate-to-severe atopic dermatitis (AD) when therapy with topical prescription medications does not provide adequate disease control or is not recommended.

2.2.3 Requested Dosage

Summary of the applied standard dosage:

The recommended dose for adult patients is an initial s.c. dose of 600 mg followed by 300 mg s.c. every other week.

For patients who achieve clear or almost clear skin after 16 weeks of treatment, dosing every fourth week may be considered.

Some patients with initial partial response may subsequently improve further with continued treatment beyond 16 weeks.

Adtralza may be used with or without topical corticosteroids, and with topical calcineurin inhibitors.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	22 January 2021
Formal control completed	27 January 2021
List of Questions (LoQ)	28 April 2021
Answers to LoQ	26 July 2021
Predecision	15 November 2021
Answers to Predecision	9 December 2021
Labelling corrections	4 February 2022
Answers to Labelling corrections	10 February 2022
Final Decision	24 February 2022
Decision	approval

3 Medical Context

Atopic dermatitis (AD) is common (affecting up to 20% of children and 8% of adults). It is defined in different ways and may not necessarily constitute a single disease entity. AD is probably a multifactorial condition in which barrier abnormalities of the skin and immunological factors play important roles. Atopic dermatitis is diagnosed on the basis of clinical criteria (primarily those proposed by Hanifin and Rajka (*Acta Dermatovener (Stockholm) Suppl. 92: 44-47, 1980*). Various scores are commonly used for determining its severity, including SCORAD and EASI.

Most cases involve mild forms that can be well controlled with simple measures and topical treatment. But persistent forms that can require costly and, in some cases, potentially burdensome systemic treatments also exist. For these reasons, the relevant guidelines recommend staged treatments.

Systemic treatments currently authorised in Switzerland:

- Dupilumab: This monoclonal IL-4/IL13 receptor inhibitor has been authorised since 2019 for the following indication "Dupixent is indicated for the treatment of moderate to severe atopic dermatitis in adults and adolescents 12 years and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not recommended".
- Cyclosporine
- Janus kinase inhibitors: Baricitinib, and upadacitinib and abrocitinib.

4 Quality Aspects

4.1 Drug Substance

Tralokinumab, the active substance of Adtralza, is a human IgG4 λ monoclonal antibody that specifically binds to human interleukin 13 (IL-13), blocking interactions with the IL-13 receptor. The antibody is composed of two identical heavy chains of 49413 Da each, and two identical light chains of 22664 Da each covalently linked with four inter-chain disulfide bonds with a molecular weight of approximately 147 kDa. Tralokinumab has an N-linked oligosaccharide attachment site in the Fc region at residue Asn-299. The oligosaccharides are predominantly fucosylated biantennary complex-type oligosaccharides.

The drug substance tralokinumab is expressed in a murine myeloma (NS0) cell line and is produced in a bioreactor. The cell culture supernatant is harvested by centrifugation, and the antibody is purified by several chromatographic and filtration steps, including virus inactivation and virus removal steps. The manufacturing process has been validated. The drug substance and its impurities were characterised using state-of-the-art methods.

The specifications include e.g. identity tests, purity and impurity tests and a bioactivity assay. All the analytical methods are described, and non-compendial methods have been validated in accordance with ICH guidelines.

Batch analysis data from non-clinical batches, clinical batches and process validation batches were provided.

Adtralza active substance is stored at -40°C . No significant changes were observed within the proposed storage conditions or under accelerated conditions. A shelf life of 60 months has been accepted.

4.2 Drug Product

Adtralza is a sterile, preservative-free, liquid dosage form presented in a single-dose, accessorised prefilled syringe intended for subcutaneous administration. Each syringe contains a label-claim of 150 mg of tralokinumab. The use of two syringes is required per 300 mg dose. The drug product at pH 5.5 contains sodium acetate/acetic acid, sodium chloride and polysorbate 80.

The manufacturing process for the finished drug product consists of pooling and mixing, filtrations, aseptic filling and stoppering, visual inspection, labelling and assembly, and packaging. Process validation was based on the evaluation of process outputs of three consecutive process validation drug substance lots to demonstrate that the process is robust and appropriate for manufacture of the drug product.

The specifications for the drug product include relevant tests and limits, e.g. for appearance such as colour of solution, strength, pH, identity, purity and impurity tests, bioactivity assay, sterility and bacterial endotoxins, and extractable volume. All non-compendial methods are validated in accordance with ICH guidelines.

Batch analysis release results from drug product lots used in the development of tralokinumab drug product from early clinical trials through to process validation lots were provided. All lots were tested using methods in place at the time of testing and met the specifications in place at the time of release.

The primary container closure system is composed of the primary packaging components: a syringe barrel, a needle, a rigid needle shield and a plunger stopper. Together these parts constitute the prefilled syringe sub-assembly, which is assembled with accessories to produce the accessorised prefilled

syringe drug product. All components coming into contact with the finished product comply with compendial standards.

The drug product is stored at 2 – 8°C protected from light. No significant changes were observed within the proposed storage conditions. A shelf life of 36 months has been accepted.

The manufacturing processes for drug substance and drug product incorporate adequate control measures to prevent contamination and maintain control with regard to viral and non-viral contaminants.

4.3 Quality Conclusions

The manufacturing processes (drug substance and drug product) are well described and demonstrate a consistent quality of drug substance and drug product. The shelf lives of the drug substance and drug product are supported by data from recommended storage conditions, as well as accelerated and stress studies. Safety aspects with regard to viral and non-viral contaminants were satisfactorily addressed. The risk for adventitious agents is minimised.

5 Nonclinical Aspects

The nonclinical development programme for Adtralza with the new active substance tralokinumab followed relevant ICH guidelines. The pivotal studies for safety assessment were performed in compliance with GLP.

5.1 Pharmacology

The affinity (K_D) of tralokinumab to human IL-13 was determined to be 58 pM. In various human cell-based *in vitro* assays, tralokinumab inhibited IL-13-dependent responses at concentrations within the picomolar to low nanomolar range (e.g. expression and/or secretion of inflammatory chemokines in keratinocytes and dermal fibroblasts, eotaxin-1 release from normal lung fibroblasts, and IgE production in peripheral blood mononuclear cells). The antibody showed high specificity for IL-13 and did not inhibit changes induced by IL-4 in the same test systems.

Tralokinumab showed *in vitro* similar neutralising potential against cynomolgus monkey IL-13 (IC_{50} 1.7 nM) and recombinant human IL-13 (IC_{50} 0.37-1.1 nM), but did not inhibit the activity of mouse IL-13. This is in line with the homology data for IL-13 (95% similarity between human and monkey, 55-62% similarity between human and mouse or rat).

In vivo pharmacology studies were conducted in mice and cynomolgus monkeys. Due to lack of cross-reactivity with murine IL-13, mice were co-administered human IL-13, which interacts with the murine receptor. The studies evaluated the effects of tralokinumab on inflammatory processes in the air pouch (mouse) or lung (mouse and monkey) since it was previously in development for asthma. The results indicate that systemic administration of tralokinumab can lead to inhibition of IL-13-dependent inflammatory responses. Since proof of concept was demonstrated in the nonclinical pharmacology studies and efficacy for the applied indication (atopic dermatitis, AD) has been evaluated in clinical studies, the lack of studies in an animal model for AD can be accepted.

Tralokinumab showed no cross-reactivity to normal human tissues, which concurs with IL-13 being a soluble target. Cross-reactivity of tralokinumab with tissues from animal species was not evaluated due to the lack of adverse findings in the toxicity studies in cynomolgus monkeys. Due to its low potential for binding to Fc receptors, the risk for induction of relevant effector functions by tralokinumab (IgG4) is considered low.

The applicant submitted adequate assessments on the potential risks for infections and carcinogenicity (see *Toxicology*) by the inhibition of IL-13 signalling. The literature review revealed a potential risk of helminthic infections, which is addressed in the information for healthcare professionals. Other potential safety risks by inhibition of IL-13 that were mentioned in the submitted literature, such as risks related to cardiovascular system, were not discussed by the applicant. In the toxicity studies in monkeys, no adverse effects on the cardiovascular system were observed up to exposures above the clinical exposure at the maximum recommended dose. It should be noted that healthy animals were used in these studies, which are not suitable for assessing possible effects of IL-13 inhibition on cardiac disease or other pathologies. Nor were any cardiovascular serious adverse events reported in the clinical studies. In female monkeys, increased glucose levels were observed after 13 weeks of subcutaneous (SC) administration of high dose tralokinumab. This could be related to the pharmacology of tralokinumab since IL-13 is involved in glucose homeostasis. However, given the isolated occurrence amongst the toxicity studies and the lack of a similar finding in the clinical trials, the risk of clinically relevant effects on glucose homeostasis is considered low.

No stand-alone safety pharmacology studies were conducted with tralokinumab, but relevant parameters were assessed in the toxicity studies. No effects on cardiovascular, respiratory or central nervous system function were observed.

5.2 Pharmacokinetics

The pharmacokinetics (PK) of tralokinumab in cynomolgus monkeys were investigated following intravenous (IV) and subcutaneous (SC) administration. Exposure generally increased in proportion to dose in the examined dose ranges (10-100 mg/kg IV or up to 300-600 mg per SC dose). T_{max} after SC dosing was within 2-7 days. Weekly administration led to a 3- to 6-fold accumulation. Terminal half-lives were similar after IV administration (12 days) and SC administration (11-17 days). The PK of tralokinumab after SC administration are comparable to the PK in humans.

In cynomolgus monkeys, tralokinumab was transferred across the placental barrier. Higher serum levels in infants from tralokinumab-treated monkeys indicate that the antibody was also excreted in milk.

In accordance with ICH S6(R1), studies on the metabolism and excretion of tralokinumab were not conducted.

All pivotal toxicity studies included evaluation of the immunogenicity of tralokinumab. ADAs were detected in some of these studies, often both in control and tralokinumab-treated groups, which was considered related to the assay performance. Based on the individual results for the different studies, only a few animals developed ADAs to tralokinumab, and the presence of ADAs was not associated with effects on exposure or adverse findings.

5.3 Toxicology

Toxicity studies with tralokinumab were conducted in cynomolgus monkeys, which is a pharmacologically relevant species (see *Pharmacology*), using either the IV or SC administration route. Doses were administered once weekly, i.e. more often than proposed for clinical use. The vehicle used in the pivotal toxicity studies is consistent with the proposed clinical formulation.

The repeat-dose studies included studies with a duration of 28 days (IV and SC), 13 weeks (IV and SC), and 26 weeks (IV). This supports the proposed chronic use in the clinic. Tralokinumab was well tolerated and there were no systemic or local adverse findings. Systemic exposures at the NOAEL doses (highest dose levels: 100 mg/kg IV or 300 mg/dose SC) were 24- to 33-fold above clinical exposure based on AUC_{0-T} .

In accordance with ICH S6(R1), no genotoxicity studies were conducted. The applicant provided an adequate justification for not conducting carcinogenicity studies and submitted an assessment on the carcinogenic potential of tralokinumab. Based on the weight of evidence, which included a review of the relevant literature from nonclinical and clinical studies and the results of the repeat-dose toxicity studies, the risk for tumorigenic potential of tralokinumab in the target patient population is considered low.

Studies to evaluate the reproductive and developmental safety profile of tralokinumab included separate fertility studies in sexually mature male and animals, a pilot embryo-fetal development (EFD) study and two enhanced pre- and postnatal developmental (ePPND) studies with 1-month or 6-month observation of the infants. Tralokinumab did not cause any effects on the evaluated fertility parameters (sperm motility, density, and morphology, menstrual cyclicality, reproductive organ weights, and histopathology). In the EFD and ePPND studies, no tralokinumab-related effects on maternal animals, gestation length or outcome, or development of fetuses and infants were observed. In the female infants from tralokinumab-treated animals, there was a slightly increased incidence of histiocytic infiltration in the spleen (minimal or mild) and increased oil-red staining in the spleen (mild); this was deemed non-adverse. Systemic exposures at the NOAEL doses in the fertility and ePPND studies (highest dose levels: 100 mg/kg IV or 350-600 mg/dose SC) were 17- to 18-fold above clinical exposure based on AUC_{0-T} . Although there were no adverse findings in these studies, the use of tralokinumab during pregnancy and lactation is not recommended due to the transfer via the placenta and/or in milk.

Local tolerance following SC administration was assessed in a dedicated study in rabbits and in the toxicity studies in monkeys. There were no adverse findings.

Tralokinumab did not induce adverse effects on general haematology, lymphocyte subsets, or immune response in adult and infant monkeys, nor were there any adverse histological findings in lymphoid tissues. Thus, the risk for immunotoxicity of tralokinumab is considered low.

The summary of the nonclinical studies in the RMP is considered adequate. As stated above, no potential safety risks were identified in these studies, which were conducted in pharmacologically relevant, healthy animals.

Since tralokinumab is a protein, it is not expected to pose a risk to the environment.

5.4 Nonclinical Conclusions

The submitted pharmacology studies showed that tralokinumab is a potent and specific inhibitor of human IL-13 and IL-13-dependent inflammatory signalling. No safety concerns were identified in an adequate set of toxicity studies in a pharmacologically relevant animal species. Potential safety risks due to the pharmacological mode of action are adequately addressed in the information for healthcare professionals. From the nonclinical standpoint, the application is approvable.

6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

Tralokinumab is an IgG4 immunoglobulin. It is assumed that tralokinumab is predominantly degraded in the reticuloendothelial system via proteolysis into small peptides and individual amino acids. Tralokinumab binds to soluble IL-13.

PK data on tralokinumab were collected in 11 phase I-III studies and analysed using a population PK analysis. The values and PK variables recorded in patients with atopic dermatitis do not deviate to any relevant extent from values recorded in subjects and patients with other diseases.

ADME

After subcutaneous administration, tralokinumab is absorbed slowly and reaches a maximum serum concentration after 5-8 days. The absolute bioavailability of tralokinumab after subcutaneous dose administration is estimated at 76% based on PopPK analyses. A dose proportionality can be assumed in the investigated range (for subcutaneous administration 45-600 mg, for intravenous administration 0.1-30 mg/kg). With the dosing regimen applied for, it can be assumed that steady-state concentrations are reached after approximately 16 weeks. The volume of distribution is estimated to be 4.2 L in the PopPK model. The estimated half-life in the PopPK model for a 75 kg patient with atopic dermatitis is 22 days. This is within the range described for other human monoclonal IgG4 antibodies.

Specific metabolism studies have not been performed.

Special Populations

In the PopPK model, up to moderate renal insufficiency (eGFR 30-89 mL/min) or mild hepatic dysfunction showed no presumed clinically relevant influence on exposure. Data sets on patients with severe renal insufficiency or at least moderate hepatic insufficiency are too small for relevant recommendations.

Interactions

No interaction studies were presented.

Pharmacodynamics

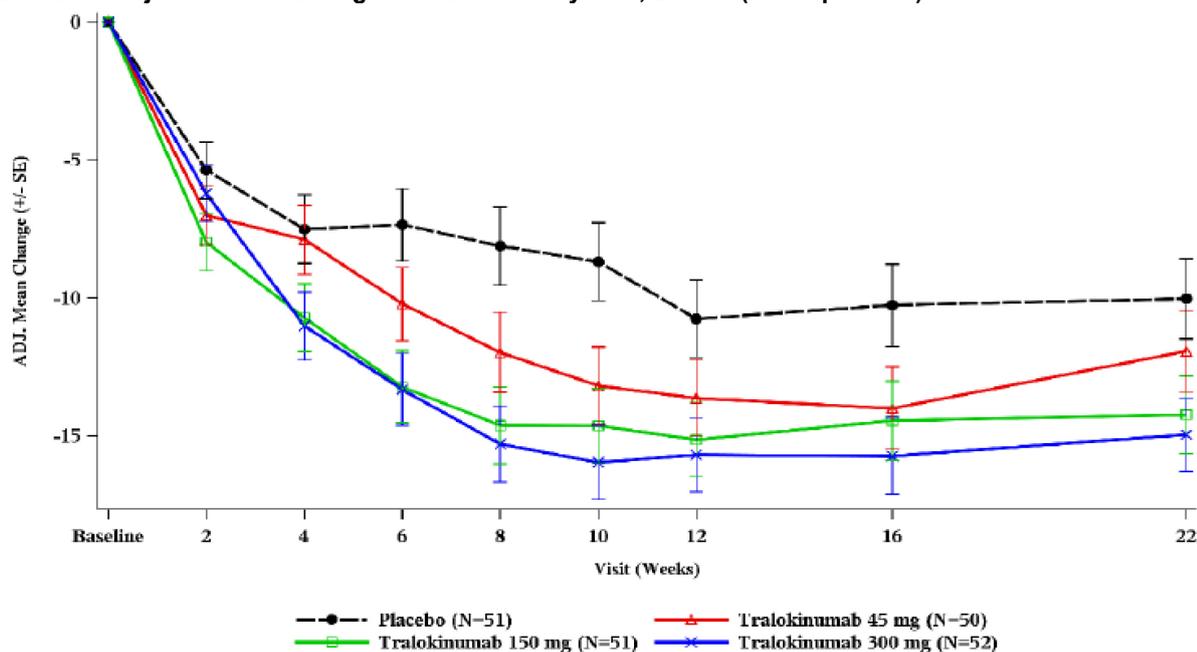
Tralokinumab is a human IgG4 monoclonal antibody that binds to interleukin-13, inhibiting IL-13 receptor binding and thus IL-13 signalling.

6.2 Dose Finding and Dose Recommendation

The dose-finding is mainly based on the 'dose-ranging' study D2213C00001. In this randomised double-blind 1:1:1 parallel group comparison, the following treatments in addition to topical corticosteroids were compared over 12 weeks in 46 patients each (40 non-Japanese and 6 Japanese):

- Tralokinumab 300 mg q2w
- Tralokinumab 150 mg q2w
- Tralokinumab 45 mg q2w
- Placebo q2w

Based on a PK/PD model, doses ≥ 300 mg were assumed to suppress IL-13 over 90%, so higher doses were not studied. Patients had moderate to severe atopic dermatitis that could not be adequately controlled with topical treatment. The primary endpoint was change from baseline in clinical score (Δ -EASI_{baseline-Week 12} in [%]) and the proportion of patients with significant clinical improvement (IGA ≤ 1 and at least a 2-grade reduction).

EASI BSA Adjusted Mean Change from Baseline by Visit, Effects (ITT Population)


In long-term extensions, numerically slightly less frequent side effects were consistently reported with administration of 300 mg at 4-weekly intervals compared with administration at 2-weekly intervals, but a slightly less favourable disease course was also reported.

Overall, the submitted clinical documentation, together with the PK data and the results of the pivotal studies, justified the requested dosing schedule.

6.3 Efficacy

The proof of efficacy was mainly based on three controlled double-blind studies in which more than 2,000 adult patients (≥ 18 years) with moderate to severe atopic dermatitis were randomised:

- Two studies with monotherapy over 16 weeks (ECZTRA 1 & 2)
- One trial of combination therapy with topical corticosteroids over 16 weeks (ECZTRA 3).

At the time of the assessment, interim results for corresponding follow-up studies with different dosing intervals (q2W + TCS versus q4W + TCS) over an additional 30-36 weeks were available.

In addition, one supportive vaccination study was presented (ECZTRA 5).

Monotherapy (ECZTRA 1 & 2)

In two randomised, double-blind, 3:1, parallel-group comparative studies with the same design, the following interventions were compared over 16 weeks in a total of 1,596 randomised patients whose atopic dermatitis could not be adequately controlled with topical treatment:

- Tralokinumab loading dose 600 mg, then 300 mg q2w;
- Placebo loading, then q2w.

Approximately one third of patients used TCS as a 'rescue' treatment during the course of the study; this proportion was higher with placebo than with tralokinumab.

Primary endpoints were proportions of patients with significant clinical improvement (IGA score of 0 or 1 at Week 16; 75% reduction from baseline in the EASI75 at Week 16). For primary and multiple-test controlled secondary endpoints, statistically significant improvements were reported for the initial 16-week phase in both tralokinumab arms compared to placebo.

	ECZTRA 1		ECZTRA 2	
	T 300 mg q2w;	Placebo	T 300 mg q2w;	Placebo
IGA ≤ 1	15.8%	7.1%	22.2%	10.9%
EASI ≥ 75	25%	12.7%	32.2%	11.4%

The differences between the treatment groups were already noticeable a few weeks after the start of treatment.

Follow-up studies:

'Responders' were re-randomised (tralokinumab 300 mg 2QW versus tralokinumab Q4W versus placebo), non-responders were treated with tralokinumab. There were numerous treatment discontinuations. At least numerically, tralokinumab performed better than placebo in the maintenance treatment: tralokinumab 300 mg 2QW ≥ tralokinumab Q4W ≥ placebo.

Combination treatment with topical corticosteroids (ECZTRA 3)

In the arm with adult patients who could not be adequately treated with topical treatment, the following interventions were compared over 16 weeks:

- TCS* + tralokinumab loading dose 600 mg, then 300 mg q2w; N = 253
- TCS* + placebo loading, then q2w N = 127

* TCS = *Mometasone furoate, 0.1% cream*.

Primary endpoints were evaluated after 16 weeks of treatment and were the same as in the monotherapy trials mentioned above. For primary and secondary endpoints, the tralokinumab arm reported a statistically significant improvement over placebo.

	T 300mg q2w;	Placebo
IGA ≤ 1	38.9%	26.2%
EASI ≥ 75	56%	35.7%

Follow-up study:

'Responders' were re-randomised (tralokinumab 300 mg 2QW versus tralokinumab Q4W versus placebo), non-responders were treated with tralokinumab. Numerically, tralokinumab performed better than placebo in maintenance treatment: tralokinumab 300 mg 2QW ≥ tralokinumab Q4W ≥ placebo.

Based on the submitted documents, a benefit of tralokinumab treatment in adult patients with moderate to severe atopic dermatitis who cannot be adequately treated with topical corticosteroids alone was concluded. In these patients, statistically significant favourable differences compared to placebo regarding acceptable efficacy endpoints were described for the tralokinumab dosage applied for, both as monotherapy and in combination with topical corticosteroids.

6.4 Safety

Vaccination study (ECZTRA 5)

Four weeks after administration of a tetanus-diphtheria-pertussis and a meningococcal vaccine, the corresponding antibody titres in 88 patients treated with tralokinumab (pre-treatment 12 weeks) were compared with the vaccination response of 78 patients treated with placebo. Numerically, antibody titers were hardly lower with tralokinumab than with placebo. However, the assay sensitivity of the

selected serological endpoints was not demonstrated, and the data presented cannot rule out possible differences in the clinically relevant vaccination response.

Patient exposure in the study programme

In placebo-controlled studies, a total of 1,991 patients receiving tralokinumab were compared with 761 patients receiving placebo. The total tralokinumab exposure in these studies corresponded to approximately 1,404 patient-years, of which about 900 patient-years were directly placebo-controlled. Placebo exposure equalled a total of 273 patient-years.

The exposure in the entire submitted clinical development of tralokinumab, including all investigated applications, was 3,054 patient-years, with a total of 4,281 exposed patients.

Adverse events

Deaths: In the placebo-controlled trials, a total of 2/1,605 deaths occurred with tralokinumab in patients with atopic dermatitis versus 0/680 with placebo. A causal relationship with the study medication is unlikely in either case.

TEAE frequency and pattern: Mild drug-related TEAEs were numerically more frequent with tralokinumab compared with placebo, whereas more severe TEAEs were less frequent. Compared to placebo, local reactions, conjunctivitis (rarely also keratitis), upper respiratory tract infections and herpes simplex, headache and blood eosinophilia were more frequent.

Antibodies: Antibodies to tralokinumab (ADAs) were evaluated in all clinical trials. ADAs were present in 4.4% of patients treated with tralokinumab and in 1.4% of tralokinumab-naïve patients. Neutralising antibodies were observed in 0.9% and 0.5% of patients, respectively. An analysis of patients with ADAs and their incidence/pattern of TEAEs does not indicate a signal.

Laboratory changes: There was a slight increase in blood eosinophilia with tralokinumab treatment, but this was usually asymptomatic.

In conclusion, mild TEAEs were slightly more frequent with tralokinumab than with placebo. The differences were mainly due to local reactions conjunctivitis/keratitis, herpes, viral infections and mild blood eosinophilia.

The experience to date is too limited to make reliable statements about rare but potentially prohibitive adverse drug reactions. Some theoretical risks of this antibody are listed below (not exhaustive):

- Tralokinumab is an IgG4 antibody and based on the dose recommendation requested, pre-existing IgG4 levels can be expected to double on average with treatment. IgG4 is quantitatively the smallest immunoglobulin subclass. With large interindividual differences (0.01-1.4mg/mL) but individually constant values, it amounts to only about 5% of the total immunoglobulins. Its function is unclear. The consequences of a permanent increase cannot be estimated at the present state of knowledge.
- Malignancy: The exact significance of IL-13, especially for tumour defence, is not known. Due to the relatively short treatment/observation period, the data presented leave the possibility of unfavourable long-term effects in this regard.

6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

The proposed application shows a clinical benefit in the population studied. This is offset above all by an unclear accumulation of conjunctivitis, slightly frequent infections with herpes and respiratory viruses, as well as theoretical risks for rare adverse effects and/or adverse effects that can only be recognised after long treatment. Although the submitted documentation showed no evidence for these theoretical risks and/or risks associated with long treatment, the safety documentation to date does not permit definite conclusions. Theoretical risks include late effects of tralokinumab-induced eosinophilia. Based on the submitted clinical and clinical pharmacology data, and in view of the significant disease burden of topically uncontrollable atopic dermatitis, a favourable risk-benefit ratio for tralokinumab treatment is considered to be demonstrated in the following indication: “Adtralza is indicated for the treatment of adult patients with moderate-to-severe atopic dermatitis (AD) when a

therapy with topical prescription medications does not provide adequate disease control or is not recommended.”

7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.

The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Adtralza was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:

The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.



This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the “Undesirable effects” section for advice on the reporting of adverse reactions.

Adtralza®

Composition

Active substances

Tralokinumab.

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

Excipients

Sodium acetate trihydrate, acetic acid 99%, sodium chloride, polysorbate 80, water for injection.

1 ml of solution for injection contains 3 mg of sodium.

Pharmaceutical form and active substance quantity per unit

Solution for injection in pre-filled syringe.

For subcutaneous injection.

The pre-filled syringe contains 150 mg tralokinumab per 1 ml (150 mg/ml).

Clear to opalescent, colourless to pale yellow solution.

Indications/Uses

Adtralza® is indicated for the treatment of adult patients with moderate-to-severe atopic dermatitis (AD) when a therapy with topical prescription medications does not provide adequate disease control or is not recommended.

Dosage/Administration

The treatment should be initiated by doctors experienced in the diagnosis and treatment of atopic dermatitis.

Usual dosage

The recommended dose of Adtralza® for adult patients is an initial dose of 600 mg (four 150 mg injections) followed by 300 mg administered every other week as subcutaneous injection (two 150 mg injections).

At the doctor's discretion, every fourth week dosing may be considered for patients who achieve clear or almost clear skin. For patients with high body weight (> 100 kg) dosage every other week may be more appropriate (see «Pharmacokinetics»).

Consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment.

Adtralza® can be used with or without topical corticosteroids. Topical calcineurin inhibitors can be used with Adtralza®.

To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Special dosage instructions

Patients with hepatic disorders

No dose adjustment is needed in patients with hepatic impairment. Very limited data are available in patients with moderate or severe hepatic impairment (see «Pharmacokinetics»).

Patients with renal disorders

No dose adjustment is needed in patients with renal impairment. Very limited data are available in patients with severe renal impairment (see «Pharmacokinetics»).

Elderly patients

No dose adjustment is recommended for elderly patients (≥ 65 years, see «Pharmacokinetics»).

Children and adolescents

The safety and efficacy of Adtralza® in children and adolescents under the age of 18 have not been investigated (see «Properties/Effects»). No data are available.

Delayed administration

If a dose is missed, administer the dose as soon as possible. Thereafter, resume dosing at the regular scheduled time.

Mode of administration

Subcutaneous use.

Adtralza® 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, administer four 150 mg Adtralza® injections consecutively in different injection sites.

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

Adtralza® can be injected by the patient or the patient's caregiver if the doctor determines that this is appropriate. Proper training should be provided to patients and/or caregivers on the preparation and administration of Adtralza® prior to use according to the Instructions for Use section in the package leaflet.

Contraindications

Hypersensitivity to the active substance or to any of the excipients according to the composition.

Warnings and precautions

Hypersensitivity reactions

If a systemic hypersensitivity reaction (immediate or delayed) occurs, administration of Adtralza® must be discontinued immediately and an appropriate therapy must be initiated.

No cases of anaphylactic reaction have been reported in a pool of five studies in atopic dermatitis.

Anaphylactic reaction has been reported very rarely in clinical studies for another indication following administration of tralokinumab.

Conjunctivitis

Patients treated with tralokinumab who develop conjunctivitis that does not resolve following standard treatment should undergo ophthalmological examination.

Helmintosis

Patients with known helminthosis 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 helminthosis should be treated before initiating treatment with Adtralza®. If patients become infected while receiving Adtralza® and do not respond to antihelminth treatment, treatment with Adtralza® must be discontinued until infection resolves.

Vaccinations

Live and live attenuated vaccines should not be given concurrently with Adtralza® as clinical safety and efficacy has not been established. The time interval between a live vaccination and the treatment with Adtralza® must comply with the current vaccination recommendations before starting therapy with immunomodulating drug substances. Immune responses to the non-live tetanus and meningococcal vaccines were assessed (see «Interactions»).

Excipients

This medicinal product contains less than 1 mmol (23 mg) sodium per 1 ml solution for injection.

Interactions

Effect of Adtralza® to other medicinal products (vaccines)

The safety and efficacy of concurrent use of Adtralza® 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) tralokinumab followed by 300 mg tralokinumab every second 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 in placebo-treated patients.

For information on live and live attenuated vaccines see «Warnings and Precautions».

Pharmacodynamic interactions

The effects of Adtralza® on the pharmacokinetics of CYP substrates have not been studied.

Pregnancy, lactation

Pregnancy

There is limited amount of data from the use of Adtralza® in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see «Preclinical Data»). Tralokinumab is not allowed to be used during pregnancy unless the potential benefit is outweighing the potential risk for the foetus.

Lactation

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 Adtralza® 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 «Preclinical Data»).

Effects on ability to drive and use machines

The influence of Adtralza® on the ability to drive and use machines has not been examined specifically.

Undesirable effects

Summary of the safety profile

The safety of Adtralza® was evaluated based on a pool of five randomised, double-blind, placebo-controlled studies in patients with moderate-to-severe atopic dermatitis including three phase 3 studies (ECZTRA 1, ECZTRA 2, ECZTRA 3), a dose-finding study and a vaccine-response study. In these five atopic dermatitis studies, 1991 patients were treated with subcutaneous injections of tralokinumab, with or without concomitant topical corticosteroids. A total of 807 patients were treated with tralokinumab for at least 1 year.

Patients who showed suicidal ideation/behaviour were excluded from the clinical trial.

The most common adverse reactions were upper respiratory tract infections (mainly common cold). In the pool of five studies in atopic dermatitis, the proportion of patients who discontinued treatment due to adverse events was 2.3% in the tralokinumab group and 2.8% in the placebo group during the initial treatment period of up to 16 weeks.

List of adverse reactions

The adverse reactions are presented according to MedDRA system organ classes and the frequency is defined as follows:

«very common» ($\geq 1/10$)

«common» ($\geq 1/100$, $< 1/10$)

«uncommon» ($\geq 1/1000$, $< 1/100$)

«rare» ($\geq 1/10'000$, $< 1/1000$)

«very rare» ($< 1/10'000$)

Within each frequency grouping undesired 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 five studies.

MedDRA System Organ Class	Frequency	Adverse Reaction
Infections and infestations	Very common (23.4%) 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 Adtralza[®] was assessed in the two monotherapy studies up to 52 weeks and in one combination study with TCS up to 32 weeks. The safety profile of Adtralza[®] through week 52 and week 32 respectively was consistent with the safety profile observed up to week 16.

Description of specific adverse reactions and additional information

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.

Most patients recovered or were recovering during the treatment period.

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.

Eosinophilia

Eosinophilia was 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. 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.

Infections

In the pool of five studies in atopic dermatitis, serious infections were reported in 0.4% of patients treated with tralokinumab and 1.1% of patients treated with placebo during the initial treatment period of up to 16 weeks.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity with tralokinumab. The incidence of anti-drug-antibodies (ADA) depends greatly on the sensitivity and specificity of the test. In addition, the observed incidence of the positivity of the antibody (including neutralising antibodies) may be influenced by several factors in a test, for example by the test methodology, the handling of the samples, the time point of sampling, the concomitant medications and the underlying disease. For these reasons, a comparison of the incidence of antibodies against tralokinumab with the incidence of antibodies against other biologics should be interpreted with caution.

In the studies ECZTRA 1, ECZTRA 2, ECZTRA 3 and the vaccine-response study, the incidence of ADA up to 16 weeks was 1.4% for patients treated with tralokinumab and 1.3% for patients treated with placebo; neutralising antibodies were seen in 0.1% of patients treated with tralokinumab and 0.2% of patients treated with placebo.

Across all trial periods, the ADA incidence for patients who received tralokinumab was 4.6%; 0.9% had persistent ADA and 1.0% had neutralizing antibodies.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the EIVIS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There is no specific treatment for Adtralza® overdose. In two clinical studies with tralokinumab in asthma, 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.

Properties/Effects

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). Tralokinumab neutralizes the biological activity of IL-13 by blocking its interaction with the IL-13R α 1/IL-4R α receptor complex.

The expression of the IL-13 cytokine and its receptors are increased in the skin of atopic dermatitis patients. Elevated levels of the IL-13 cytokine are present in the serum of atopic dermatitis patients. IL-13 signals via the IL-13R α 1/IL-4R α receptor complex and stimulates inflammatory responses, contributing to itch induction, and impairs the expression of proteins necessary for a normal skin barrier.

Pharmacodynamics

In clinical studies, treatment with Adtralza[®] was associated with decreases from baseline in concentrations of Th2 and Th22 immunity biomarkers in the blood, such as TARC/CCL17 (thymus and activation-regulated chemokine), periostin, IL-22, LDH and serum IgE. Adtralza[®] treatment was also associated with a reduced incidence of *Staphylococcus aureus* on the lesional skin.

During treatment, the addition of the IgG4 antibody tralokinumab leads to an increase in total IgG4 levels. The long-term effects of this change have not been adequately studied.

Clinical efficacy

The efficacy and safety of Adtralza[®] as monotherapy and with concomitant topical corticosteroids (TCS) were evaluated in three pivotal randomised, double-blind, placebo-controlled studies (ECZTRA 1, ECZTRA 2, ECZTRA 3) in 1976 patients 18 years of age and older with moderate to severe atopic dermatitis (AD) defined by Investigator's Global Assessment (IGA) score of 3 or 4 (moderate or severe atopic dermatitis), an Eczema Area and Severity Index (EASI) score of ≥ 16 at baseline, and a minimum body surface area (BSA) involvement of $\geq 10\%$.

Eligible patients enrolled into the three studies had previous inadequate response to topical medication. The total treatment duration was 52 weeks in ECZTRA 1 and ECZTRA 2 and 32 weeks in ECZTRA 3.

ECZTRA 1, ECZTRA 2, and ECZTRA 3 – Treatment Week 0 through Week 16

In all three studies, patients received either an initial dose of 600 mg Adtralza[®] (four 150 mg injections) on day 1, followed by 300 mg once every two weeks (Q2W) up to week 16 or matching placebo. Treatment was administered as monotherapy in ECZTRA 1 and 2 and administered with concomitant TCS in ECZTRA 3. Adtralza[®] was administered by subcutaneous (SC) injection in all studies. In ECZTRA 1, 802 patients were enrolled (199 to placebo, 603 to Adtralza[®] 300 mg Q2W). In

ECZTRA 2, 794 patients were enrolled (201 to placebo, 593 to Adtralza® 300 mg Q2W). In ECZTRA 3, 380 patients were enrolled (127 to placebo + TCS, 253 to Adtralza® 300 mg Q2W + TCS).

ECZTRA 1 and ECZTRA 2 – Treatment week 16 through week 52

In ECZTRA 1 and ECZTRA 2, to evaluate the maintenance of response, patients responding to initial 16-week treatment with Adtralza® (i.e. achieving IGA 0 or 1 or EASI-75) were re-randomised to Adtralza® 300 mg Q2W, Adtralza® 300 mg Q4W (alternating Adtralza® 300 mg and placebo Q2W), or placebo Q2W up to week 52. Patients responding to initial 16-week treatment with placebo continued to receive placebo.

Patients 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 Adtralza® 300 mg Q2W with optional use of TCS.

ECZTRA 3 – Treatment week 16 through week 32

In ECZTRA 3, to evaluate the maintenance of response, patients responding to the initial 16-week treatment with Adtralza® + TCS were re-randomised to Adtralza® 300 mg Q2W + TCS or Adtralza® 300 mg Q4W + TCS (alternating placebo 300 mg Q2W + TCS) up to 32 weeks.

Patients who responded during the initial 16-week treatment with placebo + TCS continued on placebo + TCS. Patients not achieving IGA 0 or 1 or EASI-75 at Week 16 were allocated to treatment with Adtralza® 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) and Eczema-related Sleep (NRS). Additionally, general health status assessment (SF-36) was evaluated from baseline to week 16 in ECZTRA 1 and ECZTRA 2.

Patient characteristics at start of studies

In the monotherapy studies (ECZTRA 1 and ECZTRA 2), across all treatment groups, the mean age was 37.8, 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 AD), 49.7% of patients had a baseline IGA of 4 (severe AD), 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 TCS study (ECZTRA 3), across both treatment groups, the mean age was 39.1 years, 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 randomized and dosed to Adtralza[®] 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 1).

A significant improvement in Worst Daily Pruritus NRS (mean percent change from baseline) in patients randomized to Adtralza[®] compared to placebo was observed as early as week 1 (see Figure 2). The improvement in Worst Daily Pruritus NRS occurred in conjunction with the improvement of DLQI and objective signs of atopic dermatitis including SCORAD.

Product information for human medicinal products

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

Monotherapy				
	ECZTRA 1		ECZTRA 2	
	Week 16		Week 16	
	Placebo	Adtralza® 300 mg Q2W	Placebo	Adtralza® 300 mg Q2W
<i>Number of patients randomised and dosed (FAS)</i>	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 [§]	20.4	49.9 [§]
EASI-75, % responders ^{a)}	12.7	25.0 [§]	11.4	33.2 [§]
EASI-90, % responders ^{a)}	4.1	14.5 [§]	5.5	18.3 [§]
EASI, LS mean % change from baseline (± SE)	-28.5 (± 3.66)	-51.3 [§] (± 1.92)	-22.2 (± 3.48)	-56.6 [§] (± 1.79)
SCORAD 50, % responders ^{a)}	11.7	26.0 [§]	14.4	33.5 [§]
SCORAD, LS mean %-change from baseline (± SE ^{c)}	-20.3 (2.72)	-36.7 [§] (± 1.42)	-20.6 (2.62)	-40.6 [§] (1.34)
SCORAD, LS mean change from baseline (± SE) ^{b)}	-14.7 (± 1.80)	-25.2 [§] (± 0.94)	-14.0 (± 1.79)	-28.1 [§] (± 0.92)
Pruritus NRS (≥4-point improvement, % responders) ^{a,d)}	10.3 (20/194)	20.0 [#] (119/594)	9.5 (19/200)	25.0 [§] (144/575)
Pruritus NRS, LS mean change from baseline (± SE) ^{c)}	-1.7 (± 0.21)	-2.6 [§] (± 0.11)	-1.6 (± 0.21)	-2.9 [§] (± 0.11)
DLQI (≥4-point improvement, % responders) ^{a,d)}	31.6 (60/190)	44.6 [#] (258/578)	27.3 (54/198)	56.3 [§] (325/577)
DLQI, LS mean change from baseline (± SE) ^{c)}	-5.0 (± 0.59)	-7.1 [#] (± 0.31)	-4.9 (± 0.60)	-8.8 [§] (± 0.30)

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

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

Patients who received rescue treatment or had missing data were considered non-responders in the analyses.

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

Data after initiation of rescue medication or permanent discontinuation of treatment was excluded from the analyses.

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

*p<0.05, #p< 0.01, §p<0.001

Figure 1: Mean percent change from baseline in EASI from weeks 0-16 in ECZTRA 1 and ECZTRA 2

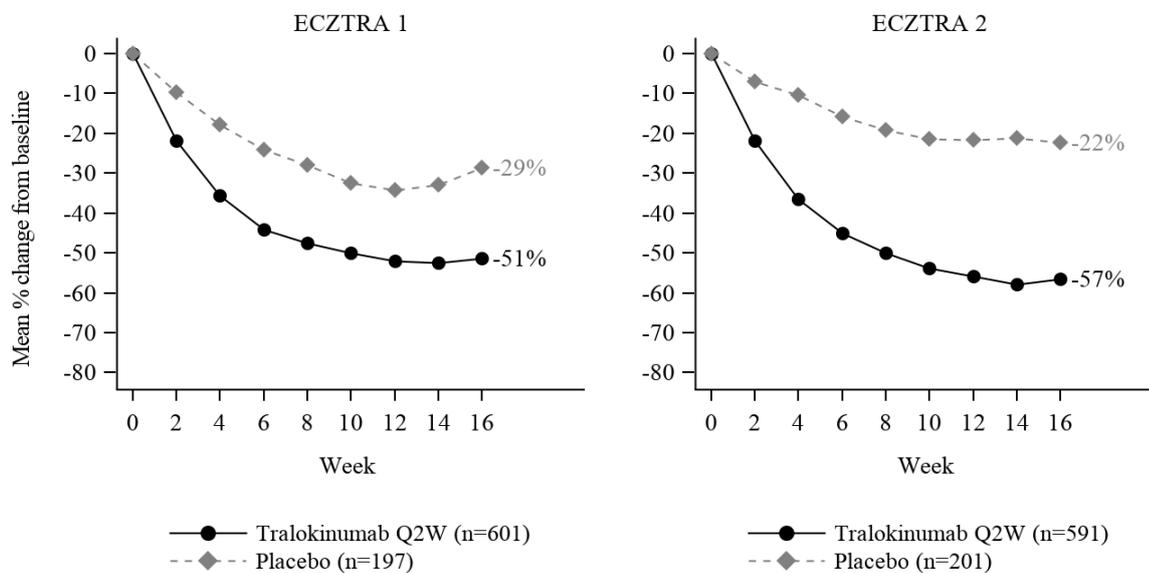
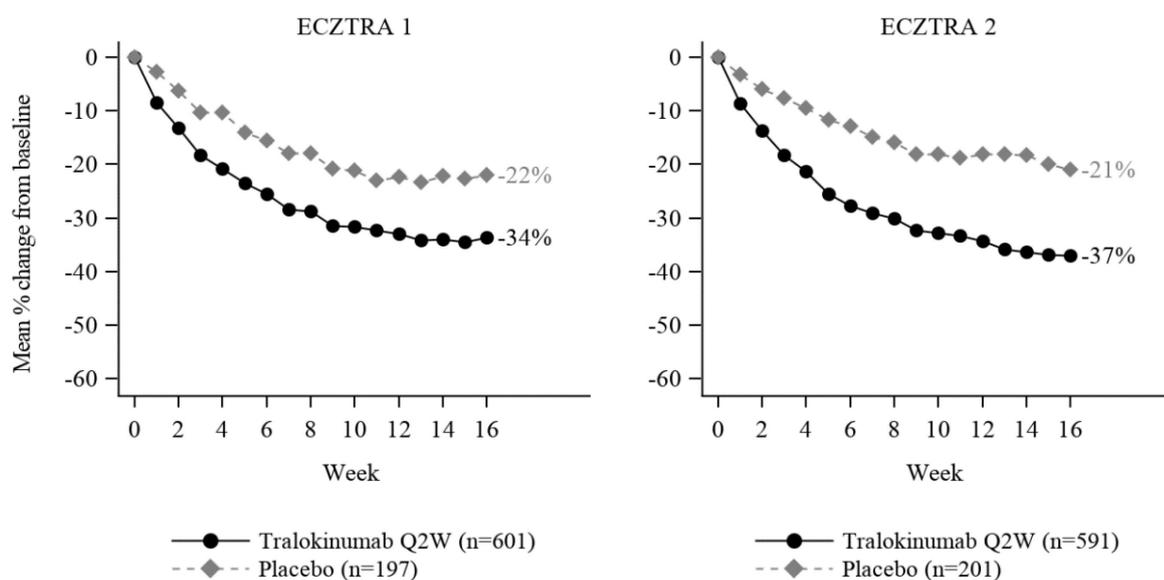


Figure 2: Mean percent change from baseline in Worst Daily Pruritus in ECZTRA 1 and ECZTRA 2



Treatment effects in subgroups (weight, age, gender, race, and prior treatment, including immunosuppressants) in ECZTRA 1 and ECZTRA 2 were consistent with the results in the overall study population.

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).

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

In table 2 the efficacy results of the responders are shown.

Table 2: Efficacy results (IGA 0 or 1 or EASI-75) at week 52 of subjects responding to Adtralza® 300 mg Q2W at week 16

Assessment at Week 52	ECZTRA 1			ECZTRA 2		
	Treatment regimen Week 16-52 ^{d)}			Treatment regimen Week 16-52 ^{d)}		
	Adtralza® 300 mg Q2W	Adtralza® 300 mg Q4W	Placebo	Adtralza® 300 mg Q2W	Adtralza® 300 mg Q4W	Placebo
IGA 0/1 ^{a)}	51.3% (20/39)	38.9% (14/36)	47.4% (9/19)	59.3% ^{c)} (32/54)	44.9% (22/49)	25.0% (7/28)
EASI-75 ^{a)}	59.6% ^{b)} (28/47)	49.1% (28/57)	33.3% (10/30)	55.8% ^{c)} (43/77)	51.4% (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=0.004 compared to placebo

c) P<0.001 compared to placebo

d) All patients were initially treated with Adtralza® 300 mg Q2W Week 0 to Week 16.

Of the patients randomised to Adtralza® who did not achieve IGA 0 or 1 or EASI-75 at week 16 and were transferred to open-label Adtralza® 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 Adtralza® treatment rather than optional TCS treatment. A higher proportion of patients with IGA 2 or EASI-50 at week 16 achieved IGA 0 or 1 or EASI-75 at week 52 compared to patients with IGA 3 or 4 or <EASI-50 at week 16.

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 Adtralza® 300 mg Q2W + TCS achieved IGA 0 or 1, EASI-75, and/or an improvement of ≥4 points on the Worst Daily Pruritus NRS from baseline to week 16 compared to placebo + TCS (see Table 3).

A significant improvement in the Worst Daily Pruritus NRS (mean percent change from baseline) in patients randomised to Adtralza® + TCS compared to placebo + TCS was observed as early as week 2 (see Figure 4). The improvement in Worst Daily Pruritus NRS occurred in conjunction with the improvement of DLQI and objective signs of atopic dermatitis including SCORAD.

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

ECZTRA 3 - Combination therapy		
	Week 16	
	Placebo + TCS	Adtralza® 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 [§]
EASI-75, % responders ^{a)}	35.7	56.0 [§]
EASI-90, % responders ^{a)}	21.4	32.9*
EASI, LS mean % change from baseline (± SE)	-55.3 (± 3.2)	-71.3 [§] (± 2.2)
SCORAD 50, % responders ^{a)}	38.1	61.1 [§]
SCORAD, LS mean %-change from baseline (± SE) ^{c)}	-40.0 (± 2.6)	-55.9 [§] (± 1.8)
SCORAD, LS mean change from baseline (± SE) ^{b)}	-26.8 (± 1.8)	-37.7 [§] (± 1.3)
Pruritus NRS (≥4-point improvement, % responders) ^{a,d)}	34.1 (43/126)	45.4* (113/249)
Pruritus NRS, LS mean change from baseline (± SE) ^{c)}	-2.9 (± 0.2)	-4.1 [§] (± 0.2)
DLQI (>4-point improvement, % responders) ^{a,d)}	65.9 (81/123)	83.5 [§] (207/248)
DLQI, LS mean change from baseline (± SE) ^{c)}	-8.8 (± 0.6)	-11.7 [§] (± 0.4)

LS=least squares; SE=standard error, FAS: Full Analysis Set - includes all patients randomized 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) Patients who received rescue treatment or had missing data were treated as non-responders in the analyses.

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 was excluded from the analyses.

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

*p<0.05, #p< 0.01, §p<0.001.

In ECZTRA 3, patients who received Adtralza® 300 mg Q2W from Week 0 to 16 used 50% less of the supplied TCS at Week 16 as compared to patients who received placebo.

Figure 3: Mean percent change from baseline in EASI in ECZTRA 3

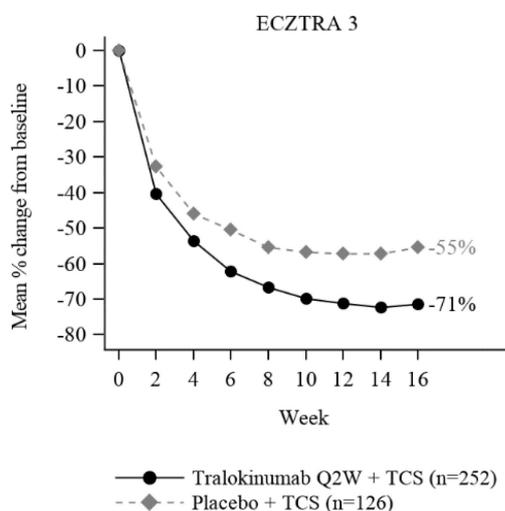
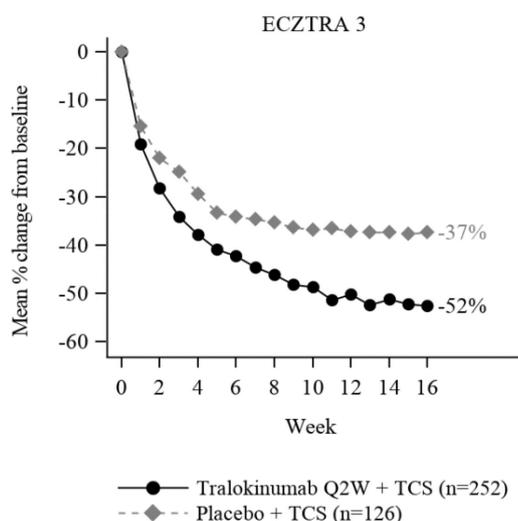


Figure 4: Mean percent change from baseline in Worst Daily Pruritus NRS (weekly average) from week 0-16 in ECZTRA 3



Treatment effects in subgroups (weight, age, gender, race, and background treatment including immunosuppressants) for the initial treatment period in ECZTRA 3 were consistent with the results in the overall study population.

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

High maintenance of clinical efficacy at week 32 were seen across Adtralza® 300 mg Q2W + TCS and Adtralza® 300 mg Q4W + TCS among patients achieving clinical response at week 16 (see Table 4).

Table 4: Efficacy results at week 32 of patients achieving clinical response of Adtralza® 300 mg + TCS Q2W at week 16

	Adtralza® 300 mg Q2W + TCS	Adtralza® 300 mg Q4W + TCS
IGA 0/1 at week 32 ^{a)}	89.6%	77.6%
% responders	(43/48)	(38/49)
EASI-75 at week 32 ^{a)}	92.5%	90.8%
% responders	(62/67)	(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)} Patients who received rescue treatment or had missing data were treated as non-responders.

The percentage is calculated relative to the number of patients with response at week 16

Among all the patients 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 Adtralza® 300 mg Q2W + TCS and 91.5% at week 32 for patients on Adtralza® 300 mg Q4W + TCS.

Of the patients randomised to Adtralza® 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 Adtralza® 300 mg Q2W + TCS for additional 16 weeks.

The continued improvement among the patients 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 5: Efficacy results of Adtralza[®] with concomitant TCS at weeks 16 and 32 in ECZTRA 3 in patients initially treated with Adtralza[®] Q2W + TCS

	Treatment regimen Week 16-32 ^{d)}					
	Responders at Week 16 ^{e)}				Non-responders at Week 16	
	Q2W + TCS		Q4W + TCS		Q2W + TCS	
<i>Patients randomised</i>	N=69		N=69		N=95	
<i>Week number</i>	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)
SCORAD, LS % mean change from baseline (SE) ^{b)}	-73.2 (2.1)	-79.2 (2.5)	-72.3 (2.1)	-73.3 (2.5)	-32.7 (1.8)	-54.5 (2.2)
Pruritus NRS (≥4-point improvement, % responders) ^{a,c)}	63.2	70.6	64.2	61.2	27.4	38.9
Pruritus NRS, mean change from baseline (SE) ^{b)}	-5.0 (0.2)	-5.4 (0.2)	-4.6 (0.2)	-4.9 (0.2)	-3.0 (0.2)	-3.7 (0.2)

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 patients with a baseline value ≥4.

^{d)} All patients were initially treated with Adtralza 300 mg Q2W + TCS from Week 0 to Week 16.

They were subsequently treated with Adtralza 300 mg Q2W + TCS or Q4W + TCS

^{e)} Responders at Week16 are identified as patients achieving either IGA 0/1 and/or EASI-75

Quality of Life/Patient-Reported Outcomes

In both monotherapy studies (ECZTRA 1 and ECZTRA 2), Adtralza[®] 300 mg Q2W improved patient-reported symptoms and the impact of AD on sleep and health-related quality of life as measured by POEM, Eczema-related sleep NRS and SF-36 were observed at week 16 compared to placebo. A higher proportion of patients administered Adtralza[®] had clinically meaningful reductions in POEM, (defined as ≥4 points improvement) from baseline to week 16 compared to placebo (see Table 6).

Product information for human medicinal products

Table 6: Other endpoints results of Adtralza® monotherapy at Week 16 in ECZTRA 1 and ECZTRA 2

Monotherapy				
	ECZTRA 1		ECZTRA 2	
	Week 16		Week 16	
	Placebo	300 mg Adtralza® Q2W	Placebo	300 mg Adtralza® Q2W
Patients randomised	199	603	201	593
Eczema-related sleep NRS, LS mean change from baseline (SE) ^{a)}	-1.9 (0.2)	-2.6 [#] (0.1)	-1.5 (0.2)	-2.9 [§] (0.1)
POEM, LS mean change from baseline (SE) ^{a)}	-3.0 (0.7)	-7.6 [§] (0.4)	-3.7 (0.7)	-8.8 [§] (0.3)
POEM (≥4-point improvement), responders ^{b)}	18.0% (35/194)	43.0% [§] (253/588)	22.1% (44/199)	54.4% [§] (319/586)
SF-36, physical component, LS mean change from baseline (SE) ^{a)}	2.9 (0.6)	4.5* (0.3)	3.2 (0.6)	5.8 [§] (0.3)
SF-36, mental component, LS mean change from baseline (SE) ^{a)}	0.3 (0.8)	2.5* (0.4)	0.5 (0.8)	3.5 [§] (0.4)

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)} Data after initiation of rescue medication or permanent discontinuation of treatment was excluded from the analyses

^{b)} Patients who received rescue treatment or had missing data were treated as non-responders.

The percentage is calculated relative to the number of patients with POEM ≥4 at baseline

*p<0.05, #p< 0.01, §p<0.001

In the concomitant TCS study (ECZTRA 3), Adtralza® 300 mg Q2W + TCS improved patient-reported symptoms and the impact of AD on sleep and health-related quality of life as measured by POEM, and Eczema-related sleep NRS were observed at week 16 compared to placebo. A higher proportion of patients administered Adtralza® had clinically meaningful reductions in POEM, (defined as ≥4 points improvement) from baseline to week 16 compared to placebo (see Table 7).

Table 7: Other endpoints results of Adtralza® with concomitant TCS at Weeks 16 in ECZTRA 3

ECZTRA 3 - Combination therapy		
	Week 16	
	Placebo + TCS	300 mg Adtralza® Q2W + TCS
Patients randomised	126	252
Eczema-related sleep NRS, LS mean change from baseline (SE) ^{a)}	-3.1 (0.2)	-4.3 [§] (0.2)
POEM, LS mean change from baseline (SE) ^{a)}	-7.8 (0.7)	-11.8 [§] (0.5)
POEM (≥4-point improvement), responders ^{b)}	59.3% (73/123)	78.4% [§] (190/250)

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)} Data after initiation of rescue medication or permanent discontinuation of treatment was excluded from the analyses

^{b)} Patients who received rescue treatment or had missing data were treated as non-responders.

The percentage is calculated relative to the number of patients with POEM >4 at baseline.

§ p<0.001

In Adtralza® 300 mg Q2W + TCS responders at week 16, who were maintained on Adtralza® 300 mg Q2W + TCS or Q4W + TCS, clinically meaningful reductions in POEM, DLQI and Eczema-related sleep NRS were observed from baseline to week 32.

Table 8: Other endpoints results of Adtralza® with concomitant TCS at Weeks 16 and 32 in ECZTRA 3 in patients achieving clinical response at Week 16

	Treatment regimen Week 16-32 ^{a)}			
	Responders at Week 16 ^{b)}			
	Adtralza® Q2W + TCS		Adtralza® Q4W + TCS	
<i>Patients randomised</i>	N=69		N=69	
<i>Week number</i>	W16	W32	W16	W32
DLQI, LS mean change from baseline (SE) ^{c)}	-14.0 (0.6)	-14.6 (0.6)	-13.9 (0.6)	-13.7 (0.6)
POEM, LS mean change from baseline (SE) ^{c)}	-15.2 (0.7)	-15.6 (0.7)	-14.1 (0.7)	-13.9 (0.8)
Eczema-related sleep NRS, LS mean change from baseline (SE) ^{c)}	-5.2 (0.2)	-5.5 (0.2)	-4.8 (0.2)	-5.2 (0.3)
DLQI (≥4-point improvement), % responders ^{d)}	98.5% (65/66)	89.4% (59/66)	100.0% (68/68)	83.8% (57/68)
POEM (≥4-point improvement), % responders ^{d)}	89.7% (61/68)	88.2% (60/68)	94.1% (64/68)	83.8% (57/68)

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)} All patients were initially treated with Adtralza 300 mg Q2W + TCS from Week 0 to Week 16. They were subsequently treated with Adtralza 300 mg Q2W + TCS or Q4W + TCS

^{b)} Responders at Week16 are identified as patients achieving either IGA 0/1 and/or EASI-75.

^{c)} Data after initiation of rescue medication or permanent discontinuation of treatment was excluded from the analyses.

^{d)} Number of responders divided by number of patients having baseline value >4 of the given parameter.

Patients who received rescue treatment or had missing data were treated as non-responders.

Pharmacokinetics

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 is 76%.

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.

Metabolism

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.

Linearity/non-linearity

Exposure of tralokinumab increases proportionally to the dose of tralokinumab over a wide range of investigated doses 0.1-30 mg/kg.

Kinetics in specific patient groups

Gender

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

Body weight

Tralokinumab trough concentrations were lower in patients with higher body weight.

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. Moderate or severe hepatic impairment was not found to affect the PK of tralokinumab. 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.

Elderly patients

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

Children and adolescents

The pharmacokinetics of tralokinumab in paediatric patients has not yet been studied.

Genetic polymorphisms

Population pharmacokinetics analysis revealed no association between ethnicity and clinically significant effects on systemic exposure to Adtralza®.

Preclinical data

Repeated dose toxicity

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.

Mutagenicity

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

Carcinogenicity

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.

Reproductive toxicity

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 weekly with tralokinumab subcutaneously up to 350 mg (females) or 600 mg (males). The exposure (AUC) of the animals in these studies was about 17-fold higher than the clinical exposure.

Other information

Incompatibilities

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

Shelf life

Do not use this medicine after the expiry date («EXP») stated on the pack.

Shelf life after opening

As the medicine does not contain a preservative, any unused medicine left in the pre-filled syringe should be discarded.

Special precautions for storage

Store in the refrigerator (2-8°C).

Do not freeze.

Store in the original outer packaging to protect from heat and direct sun light.

Keep out of the reach of children.

If necessary, pre-filled syringes may be kept at room temperature up to 25°C for a maximum of 14 days. If the carton needs to be removed permanently from refrigerator, the date of removal may be recorded on the outer carton.

After removal from the refrigerator, the medicinal product must be used within 14 days or discarded.

The pre-filled syringe should not be exposed to heat or direct sunlight and should not be shaken.

Instructions for handling

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

After removing the pre-filled syringe from the refrigerator, it should be allowed to reach room temperature by waiting for 30 min before injecting Adtralza®.

The pre-filled syringes are for single use only.

Authorisation number

68229 (Swissmedic)

Packs

Adtralza®, solution for injection in pre-filled syringe with 1 ml solution:

1 multipack containing totally 4 pre-filled syringes (2 single packs with 2 pre-filled syringe each). [B]

Marketing authorisation holder

Leo Pharmaceutical Products Sarath Ltd., Regensdorf ZH

Date of revision of the text

November 2021