15 September 2022
EMA/CHMP/742229/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Adtralza

International non-proprietary name: tralokinumab

Procedure No. EMEA/H/C/005255/II/0002

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

AD	atopic dermatitis
ADA	anti-drug antibody(ies)
AD pool	data pool including the ECZTRA 1, 2, 3, 5, and D2213C00001 tralokinumab trials in subjects with AD
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
BAA	Black or African American
CCL17	C-C motif chemokine ligand 17 (also known as thymus- and activation-regulated chemokine, TARC)
CDLQI	Children's Dermatology Life Quality Index
CD-RI-CAT-354-1054	a completed tralokinumab phase 1 single-dose trial in adolescent subjects with asthma
D2213C00001	a completed phase 2 dose-finding trial evaluating the efficacy of tralokinumab in combination with TCS
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EASI50/75/90	at least 50/75/90% reduction in EASI score
ECG	electrocardiogram
ECZTEND	an ongoing phase 3 extension trial in subjects with moderate-to-severe AD, including adolescent subjects who completed ECZTRA 6 and who will receive tralokinumab for up to 2.2 years in ECZTEND (LP0162-1337)
ECZTRA 1	a completed tralokinumab phase 3 monotherapy trial in adult subjects with AD (LP0162-1325)
ECZTRA 2	a completed tralokinumab phase 3 monotherapy trial in adult subjects with AD (LP0162-1326)
ECZTRA 3	a completed tralokinumab phase 3 combination trial in adult subjects with AD, where tralokinumab was given in combination with TCS (LP0162-1339)
ECZTRA 5	a completed tralokinumab phase 2 vaccine response trial in adult subjects with AD, where the immune response to vaccines administered concomitantly with tralokinumab was investigated (LP0162-1341)
ECZTRA 6	a completed phase 3 trial in adolescent subjects with moderate-to-severe AD who received tralokinumab or placebo for up to 52 weeks (LP0162-1334)
EMA	European Medicines Agency
EU	European Union

FDA	Food and Drug Administration (US)
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IGA	Investigator's Global Assessment
IgE	immunoglobulin E
IL	interleukin
IMP	investigational medicinal product
JAK	Janus kinase
MCID	minimum clinically important differences
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
mRNA	messenger ribonucleic acid
nAb	neutralising antibody(ies)
NRS	numeric rating scale
PD	pharmacodynamic(s)
PDCO	Paediatric Committee (EMA)
PIP	paediatric investigation plan
PK	pharmacokinetic(s)
POEM	Patient-Oriented Eczema Measure
PRO	patient-reported outcome
PSP	pediatric study plan
PT	preferred term
PYE	patient years of exposure
Q2W	every 2 weeks
Q4W	every 4 weeks
SAE	serious adverse event
SC	subcutaneous
SCORAD	Scoring Atopic Dermatitis
SOC	system organ class
TCI	topical calcineurin inhibitors
TCS	topical corticosteroid
UK	United Kingdom

US	United States of America

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, LEO Pharma A/S submitted to the European Medicines Agency on 23 November 2021 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of adolescent patients (12-17 years) for Adtralza based on final study LP0162-1334 (ECZTRA 6): a multicentre, randomised, double-blind, placebo-controlled study in adolescent patients 12 to 17 years of age with moderate-to-severe atopic dermatitis to evaluate the efficacy and safety of tralokinumab monotherapy in this population group. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0292/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0292/2021 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Not applicable.

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jayne Crowe Co-Rapporteur: <N/A>

Timetable	Actual dates
Submission date	23 November 2021
Start of procedure:	25 December 2021
CHMP Rapporteur Assessment Report	18 February 2022
CHMP members comments	14 March 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report	16 March 2022
Request for supplementary information (RSI)	24 March 2022
CHMP Rapporteur Assessment Report	22 August 2022
CHMP members comments	5 September 2022
Updated CHMP Rapporteur Assessment Report	7 September 2022
Opinion	15 September 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Adolescents, atopic dermatitis

Atopic dermatitis (AD) is the most common inflammatory skin disease in the developed world. It is more common in paediatric populations than in adults, with the 1-year prevalence in adolescents estimated to be approximately 15–20%. Although AD usually presents as mild disease in the paediatric population, around 10–30% of children with AD have moderate-to-severe disease.

Disease signs and symptoms in moderate-to-severe AD are characterised by intense itch, xerosis, and recurrent eczematous skin lesions. In children from 2 years of age to puberty, AD typically involves the flexural surfaces of the extremities, head, neck, wrists, and ankles.

In adolescents and adults, eczematous changes are typically seen on the head and neck, flexural surfaces of the extremities, and hands and feet. These signs and symptoms cause substantial morbidity and have a serious impact on the psychological wellbeing and health-related quality of life in affected children and their families. Compared with adolescents who do not have AD, adolescents with AD are at higher risk of the most common psychiatric conditions, including depression and anxiety, and this risk increases with increasing AD severity. Furthermore, children with AD are at higher risk of learning disabilities – with potential lifelong implications for health, educational, and social outcomes – and this risk also increases with increasing AD severity. An important treatment goal for patients in this vulnerable period of life is therefore to also improve their psychosocial wellbeing and ability to function in daily life.

The MAH's initially claimed therapeutic indication was:

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.

Epidemiology

Atopic dermatitis (AD) is a chronic inflammatory skin disorder that typically occurs during childhood especially in the first year of life, with a variable frequency from 10% to 30%. Recent studies have shown that in Europe among 10–20% of children with AD suffer from this disorder also in adolescence. AD prevalence in adolescence has been estimated around 5–15% in European countries.

Biologic features, Aetiology and pathogenesis

The pathogenesis of AD is a complex interplay between genetic predisposition, the environment, skin barrier dysfunction, and immune dysregulation. The immune dysregulation is predominantly driven by Th2 lymphocytes that can be found in abundance in AD skin lesions together with increased levels of Th2-derived cytokines, such as IL-13.

IL-13 is a cytokine with a prominent role in the altered immune response in AD. IL-13 is overexpressed in lesional and non-lesional skin in patients with AD compared to normal skin, and both IL-13 mRNA expression and protein levels correlate with disease severity. Correspondingly, sub-clinical inflammation, including increased IL-13 mRNA and skin barrier function impairment are also seen in non-lesional skin in subjects with AD, compared with that seen in normal skin. IL-13 plays a prominent role in inflammation, epidermal barrier dysfunction and pathogen persistence in lesional skin, as IL-13 acts directly on keratinocytes to: stimulate keratinocytes to secrete chemokines and cytokines that attract more immune cells and amplify the inflammatory response, which further disrupts the skin barrier by reducing the expression of skin barrier proteins and lipids; increase pathogen persistence by down-regulating the production of antimicrobial peptides, such as beta-defensin and cathelicidin. Although IL-13 is believed to increase pathogen persistence by down-regulating the production of antimicrobial peptides, studies have shown that these defence molecules are increased in AD skin and correlate with disease severity. These molecules have pro-inflammatory properties by inducing the production of IL-4, IL-13, and IL-31, thereby contributing to the pathogenesis of AD. Finally, IL-13 activates itch signalling by stimulating peripheral itch-sensory neurons.

These effects of IL-13 have a complex interplay. Decreased barrier function and pathogen persistence facilitates allergen and pathogen entry into the skin, which causes additional immune activation and inflammation. IL-13 also drives IgE production and contributes to mast cell activation, and once allergens are cross-linked to IgE on the mast cell surface, histamine release and itch are further induced. This leads to a vicious cycle of itch-induced scratching, leading to mechanical skin barrier defects that facilitate entry of more antigens and pathogens, thereby promoting further immune activation. Skin infections are a major complication for patients with moderate-to-severe AD. A compromised skin barrier function and a Th2-dominated immune response are considered risk factors that contribute to the susceptibility to both viral and bacterial infections, which patients with AD are prone to. In addition to these factors, 80-100% of patients with AD are colonised with S. aureus on active lesions, whereas only 5-30% of normal individuals are colonised with S. aureus. On the individual level, S. aureus colonisation can lead to S. aureus skin infections (impetigo and cellulitis) and worsening of AD. Viral infections (herpes simplex and pox virus) are more common in patients with AD, and eczema herpeticum, a severe widespread infection of herpes simplex virus, is mainly seen in patients severely affected by AD.

Clinical presentation and diagnosis

Patients with moderate-to-severe AD report symptoms such as itch, excessive dryness or scaling, red or inflamed skin, blisters or bumps, and open sores or oozing. All these symptoms can be debilitating and associated with pain, sleep disturbance, and impaired social functioning. The patient burden of disease relates directly to the physical signs and symptoms of disease (e.g. pruritus and pain) as well as indirectly to the harmful impact of skin symptoms on sleep (e.g. difficulty falling asleep, more frequent awakenings, prolonged awakenings and fragmented sleep), mental health, concentration, physical activity and sedentary behaviour, activities of daily living, performance at school and work, increased number of sick days and missed days of work.

More than half of patients with moderate-to-severe AD have been reported to suffer from depression and anxiety. Emotional distress resulting from AD, such as embarrassment, low self-esteem, and difficulties establishing and maintaining relationships, is also frequently reported. One in two adults with severe AD report that AD causes them to avoid social interaction because of their appearance and that AD impacts their activities quite a bit or a great deal. Furthermore, AD can be a very time-consuming condition to manage. Patients can spend over an hour each day on their treatment regimens.

In the Global Burden of Disease Study 2013, skin diseases were the fourth largest cause of disability worldwide with dermatitis, including AD, being the most burdensome skin disease.

Management

Standard treatment for AD in adolescents is similar to that in adults, typically progressing in accordance with disease severity from mild topical anti-inflammatory therapy to high-potency topical therapy and in some cases systemic immunomodulatory therapy.

Panel 1 ***Current therapies approved for atopic dermatitis in paediatric patients, by region/country, disease severity, and age group***

Therapy	Region/country[a]	AD severity	Paediatric age group
Topical corticosteroids[b]	All	Mild-to-severe	All
Topical calcineurin inhibitors			
Pimecrolimus	EU, UK	Mild-to-moderate	>2 years
	Canada	Mild-to-moderate	≥3 months
Tacrolimus	EU, UK, Canada	Moderate-to-severe	>2 years
Cyclosporine	UK	Severe	Not recommended for treatment of AD in children <16 years
Dupilumab	EU, UK	Severe	6–11 years
	EU, UK	Moderate-to-severe	≥12 years
	US, Canada	Moderate-to-severe	≥6 years
Janus kinase inhibitors			
Abrocitinib	UK	Moderate-to-severe	≥12 years
Ruxolitinib	US	Mild-to-moderate	≥12 years
Upadacitinib	EU, UK, Canada	Moderate-to-severe	≥12 years

TCS and TCI have limited efficacy in patients with moderate-to-severe disease. High-potency TCS, as well as systemic therapies except for the newer biologics and JAK inhibitors, are reserved for severe disease and are associated with significant safety concerns, especially in children and when used long-term. Cyclosporine, for instance, has common and severe side effects such as nephrotoxicity, hepatotoxicity, and hypertension. Cyclosporine is therefore only approved for the treatment of severe AD and is only recommended for patients where the expected clinical benefit outweighs the risk of side effects. Some

drugs in the JAK inhibitor drug class, including upadacitinib and ruxolitinib, have a black box warning by the FDA about increased risk of serious infections, heart-related events, cancer, blood clots and death. As AD is a heterogenous, chronic disease characterised by flares and exacerbations, multiple treatment options are necessary for adequate long-term disease management. Dupilumab is currently the only selective immunomodulating biologic therapy available for the treatment of AD in adolescents. However, some patients have inadequate response or unacceptable side effects with dupilumab. Hence, there is a need for additional well-tolerated treatments that target the underlying cause of AD and offer long-term disease control without intolerable side effects.

2.1.2. About the product

Tralokinumab 150 mg solution for injection was approved by the European Commission on 17-Jun-2021 under the name of Adtralza for the treatment of moderate-to-severe AD in adult patients, who are candidates for systemic therapy. The recommended dosage of tralokinumab in adults is an initial dose of 600 mg followed by 300 mg administered every 2 weeks by SC injection. Tralokinumab can be used with or without TCS.

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.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

ECZTRA 6 was conducted in accordance with the PIP (EMEA-001900-PIP02-17), as agreed with the PDCO. Meetings to discuss the PIP were held with the PDCO on 28-Sep-2017 and 07-Sep-2018.

2.1.4. General comments on compliance with GCP

The data supporting the use of tralokinumab in adolescents derive from 1 pivotal trial and 2 supportive trials, as outlined below. The applicant stated that the trials were conducted in accordance with the ICH guidance on GCP.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

As a monoclonal antibody, tralokinumab is exempt from testing in accordance with the current CHMP guideline (CHMP/SWP/4447/00) on environmental risk assessment.

2.2.2. Conclusions on the non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Trial ID	EudraCT No	Protocol Title	EU Countries involved	Non-EU Countries involved	CTR presented in Section
Atopic dermatitis					
LP0162-1334	2017-005143-33	Tralokinumab monotherapy for adolescent subjects with moderate-to-severe atopic dermatitis. ECZTRA 6 (ECZema TRAlokinumab trial no. 6)	Belgium France Germany Netherlands Poland	Australia Canada Great Britain Japan United States	M.5.3.5.1

Supportive trials:

• ECZTEND – an ongoing phase 3 extension trial in subjects with moderate-to-severe AD, including adolescent subjects who completed ECZTRA 6 and who will receive tralokinumab 300 mg Q2W open-label in ECZTEND. As this trial is ongoing, only information on exposure, SAEs, and AEs leading to permanent discontinuation of IMP for the adolescent subjects transferred from ECZTRA 6 is included in this application as additional long-term safety data. The data cut-off for the safety data from ECZTEND is 31-Mar-2021.

• CD-RI-CAT-354-1054 – a completed phase 1 trial in adolescent subjects with asthma who received a single dose of tralokinumab 300 mg.

2.3.2. Pharmacokinetics

Tralokinumab is a fully human IgG4 monoclonal antibody that specifically neutralises the IL-13 cytokine by inhibiting the interactions with the IL-13 receptors. The target population in this submission is adolescent subjects with moderate-to-severe atopic dermatitis (AD). The intended route of administration of tralokinumab is SC injection.

The recommended dosage of tralokinumab in adults is an initial dose of 600 mg followed by 300 mg administered every 2 weeks by SC injection. The same dose is proposed for adolescent patients with AD.

To date, data on the clinical pharmacology of tralokinumab in adolescent subjects are available from 2 completed clinical trials, which are included in this assessment. In addition, the PK data from these 2 trials have been incorporated into the previously developed population PK model that was based on data from adult subjects.

• ECZTRA 6 – a phase 3 trial in adolescent subjects with moderate-to-severe AD who received tralokinumab (300 mg or 150 mg) or placebo for up to 52 weeks. The clinical pharmacology evaluation in this trial included PK (tralokinumab trough concentrations), PD (key AD biomarkers), and immunogenicity (ADA).

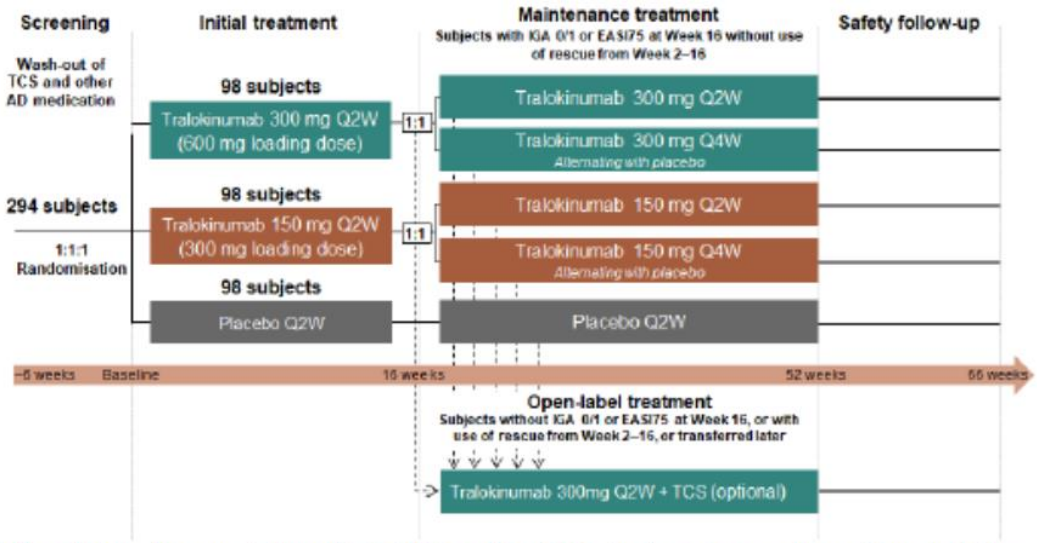
• CD-RI-CAT-354-1054 – a phase 1 trial in adolescent subjects with asthma who received a single dose of tralokinumab (300 mg). The clinical pharmacology evaluation in this trial included PK profiling (rich sampling) and immunogenicity (ADA).

The bioanalytical methods used in the trials for the present application were the same as those previously assessed for the initial application.

ECZTRA 6 (LP0162-1334)

This was a randomised, double-blind, placebo-controlled, parallel-group trial in adolescent subjects with moderate-to-severe AD who are candidates for systemic therapy. The trial design is shown in Panel 2.

Panel 2 ***Trial design of ECZTRA 6***



Abbreviations: AD = atopic dermatitis; EASI75 = at least 75% reduction in Eczema Area and Severity Index score; IGA 0/1 = Investigator's Global Assessment response of 0 (clear) or 1 (almost clear); Q2W = every 2 weeks; Q4W = every 4 weeks; TCS = topical corticosteroids.

Serum samples for assessment of tralokinumab trough concentrations were collected at Week 4, 16, 28, 52 and 66. Samples for assessment of ADA were collected at the same time points as well as at Week 0.

Results

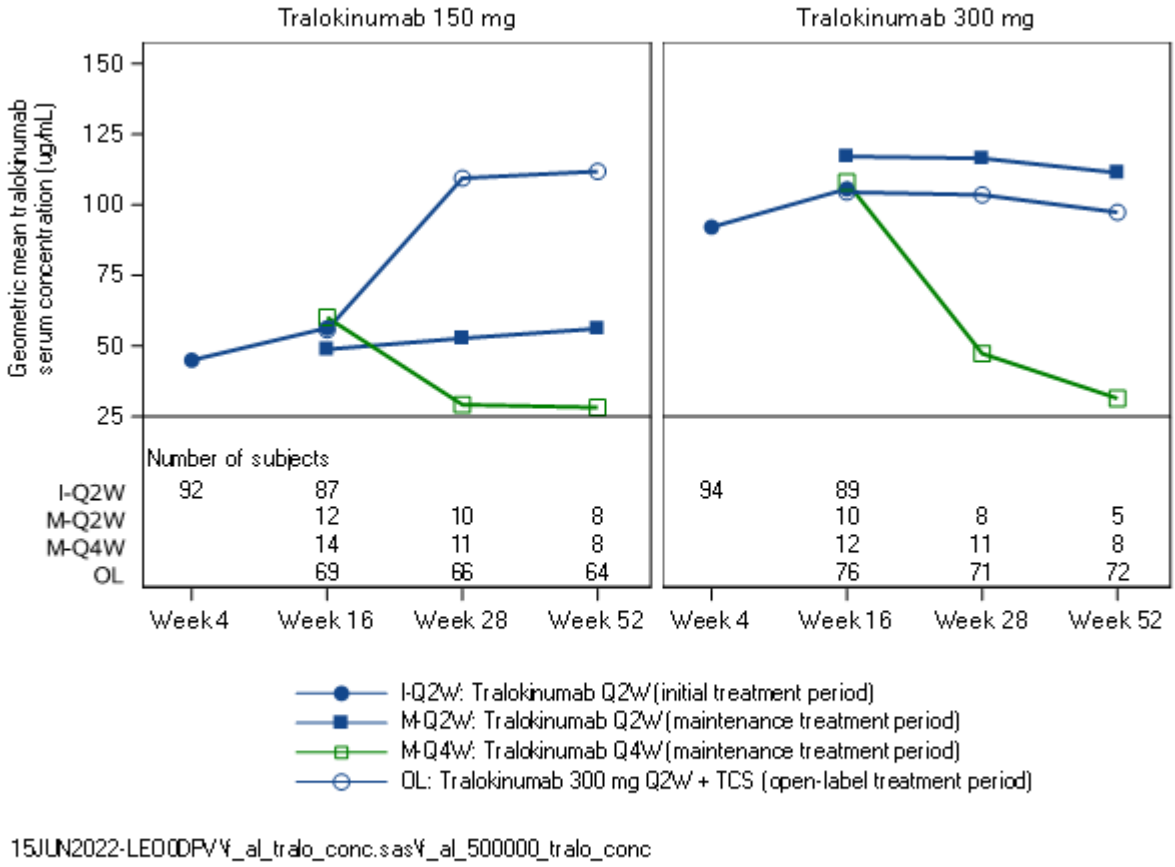
A total of 276 subjects received at least 1 dose of tralokinumab. The demographic data were generally similar across treatment groups. In the full analysis set, 57% of the subjects were white, 25% were Asian, and 11% were Black or African American. Most of the subjects were not Hispanic or Latino, and just over half were male. The median age was 15.0 years (mean: 14.6; SD: 1.7), the mean body weight was 61.5 kg (SD: 17.4, range: 30–144), and the mean BMI was 22.9 kg/m2 (SD: 5.3, range: 14.3–57.6).

Pharmacokinetics

An initial loading dose of tralokinumab (600 mg for the tralokinumab 300 mg Q2W group and 300 mg for the tralokinumab 150 mg Q2W group) was given at Week 0. Panel 3 shows the geometric mean trough concentrations of tralokinumab over time for the different dosing regimens.

ECZTRA 6

Panel 3 ***ECZTRA 6 – mean trough concentrations of tralokinumab after subcutaneous dosing every 2 or 4 weeks for up to 52 weeks, shown by initial treatment (150 mg or 300 mg): safety analysis set***



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Abbreviations: I = initial treatment period; M = maintenance treatment period; OL = open-label; Q2W = every 2 weeks; Q4W = every 4 weeks; TCS = topical corticosteroids.

For the subjects receiving tralokinumab 150 mg Q2W in the initial treatment period (left side of Panel 3), tralokinumab serum concentrations had reached steady state by Week 16. The geometric mean trough concentration at the previous sampling time point at Week 4 was close to that at Week 16, owing to the initial loading dose at baseline. For the responders who were re-randomised at Week 16 to maintenance treatment with tralokinumab 150 mg Q2W, the trough concentration remained stable throughout the maintenance period (filled blue squares). For the responders who were re-randomised to Q4W, the trough concentration was approximately halved by the next sampling time point at Week 28 (open green squares), consistent with linear PK. Conversely, for the tralokinumab 150 mg non-responders who were transferred at Week 16 to open-label tralokinumab 300 mg Q2W (open blue circles), the trough concentration was approximately doubled by Week 28 and was similar to the concentrations in the other subjects receiving 300 mg Q2W (right side of the Panel 3).

For the subjects receiving tralokinumab 300 mg Q2W in the initial treatment period (right side of Panel 3), the pattern in the initial and maintenance treatment periods was similar to that described above, with trough concentrations approximately the double of those in the corresponding tralokinumab 150 mg groups. A divergence from this expected pattern was the low trough concentration at Week 52 in the tralokinumab 300 mg Q4W group. This result could be due to the small number of subjects. Furthermore, for the tralokinumab 300 mg non-responders who were transferred at Week 16 to open-label

tralokinumab 300 mg Q2W, the mean trough concentrations were slightly lower than the trough concentrations for tralokinumab responders receiving tralokinumab 300 mg Q2W.

For the subjects receiving placebo in the initial treatment period who transferred at Week 16 to open-label tralokinumab 300 mg Q2W (i.e. placebo non-responders), the mean concentrations at Week 28 and Week 52 were comparable with those for tralokinumab 300 mg non-responders.

Comparison between adolescents and adults

The steady-state trough concentration in the tralokinumab 300 mg group was higher in ECZTRA 6 than that in the tralokinumab phase 3 monotherapy trials in adult subjects, ECZTRA 1 and ECZTRA 2. The geometric mean serum concentration of tralokinumab 300 mg at Week 16 in the adolescent and adult monotherapy trials were:

• 105.7 μg/mL (CV: 39.0%, n=97) in ECZTRA 6 (adolescents).

• 88.4 μg/mL (CV: 66.1%, n=602) in ECZTRA 1 (adults).

• 90.7 μg/mL (CV: 59.3%, n=592) in ECZTRA 2 (adults).

The difference is most likely related to the lower mean body weight in adolescents than in adults, which is consistent with the known relationship between tralokinumab exposure and body weight: steady-state exposure decreases with increasing body weight.

Immunogenicity

During the initial treatment period, 7 (7.1%) of the subjects treated with tralokinumab 150 mg, none of the subjects treated with tralokinumab 300 mg, and 2 (2.1%) of the subjects treated with placebo had treatment-emergent ADA.

During the entire trial, 20 (7.3%) tralokinumab-treated subjects had a treatment-emergent ADA response, which was persistent for 4 (1.5%) subjects, indeterminate for 10 (3.6%) subjects, and transient for 6 (2.2%) subjects. 1 (0.4%) tralokinumab-treated subject had treatment-boosted ADA. 2 (2.1%) of the tralokinumab-naïve subjects had a treatment-emergent ADA response, which was indeterminate in both cases.

2 (0.7%) tralokinumab-treated subjects tested positive for nAb, which was deemed not to have an impact on the PK, efficacy, or safety of tralokinumab for these subjects.

Comparison between adolescents and adults

The main ADA findings in ECZTRA 6 are summarised in

Panel 4, along with those reported in the integrated immunogenicity evaluation for the adult population based on the ADA ECZTRA analysis set (covering ECZTRA 1, 2, 3, and 5). Owing to the low number of ADA-positive subjects in ECZTRA 6, it is not meaningful to compare the incidence for tralokinumab 150 mg and tralokinumab 300 mg in the initial treatment period.

Panel 4 ***Anti-drug antibodies in ECZTRA 6 ADA ECZTRA analysis set***

Trial period ADA status	ECZTRA 6 (adolescents)			ADA ECZTRA analysis set[a] (adults)	
Initial treatment	Tralokinumab		Placebo (N=94)	Tralokinumab 300 mg (N=1553)	Placebo (N=629)
	150 mg (N=98)	300 mg (N=97)			
Treatment-emergent[b]	7 (7.1%)	0	2 (2.1%)	21 (1.4%)	8 (1.3%)
Entire trial	Tralokinumab-treated (N=275)		Tralokinumab-naïve (N=94)	Tralokinumab-treated (N=1939)	Tralokinumab-naïve (N=629)
Treatment-boosted[c]	1 (0.4%)			3 (0.2%)	
Treatment-emergent[b]	20 (7.3%)		2 (2.1%)	87 (4.5%)	9 (1.4%)
Persistent[d]	4 (1.5%)			17 (0.9%)	1 (0.2%)

Note: a = all subjects treated in the ECZTRA 1, 2, 3, and 5 trials; b = ADA-negative or missing at baseline and at least 1 positive post-baseline ADA response; c = ADA-positive at baseline and at least 1 post-baseline ADA response ≥4-fold over baseline titre level; d = ADA-positive for at least 2 consecutive visits at least 10 weeks apart.

Abbreviations: ADA = anti-drug antibodies.

For all subjects with positive ADA status, ADA titres were generally low, ranging from <10–320 in ECZTRA 6 and from <10–640 in the ADA ECZTRA analysis set. Among tralokinumab-treated subjects, 2 (0.7%) subjects in ECZTRA 6 and 19 (1.0%) subjects in the ADA ECZTRA analysis set tested positive for nAb.

Thus, the immunogenicity results observed for the adolescent subjects in ECZTRA 6 are comparable with those reported for the adult population. The proportion of subjects with treatment-emergent ADA is higher in ECZTRA 6, including for placebo-treated subjects. ADA titres and the rate of nAb are similarly low in the adolescent and adult trial populations and were deemed not to have an impact on the PK, efficacy, or safety of tralokinumab.

Study CD-RI-CAT-354-1054

This was an open-label, single-dose trial to evaluate the PK profile of a single SC dose of tralokinumab 300 mg in adolescent subjects with asthma. Immunogenicity was assessed as a secondary objective.

Blood samples were collected over the first 24 hours (immediately predose and 3, 8, and 24 hours ± 30 minutes post-dose), then on Days 4, 6, 8, and Weeks 2, 3, 5, and 8.

PK parameters were calculated using non-compartmental methods.

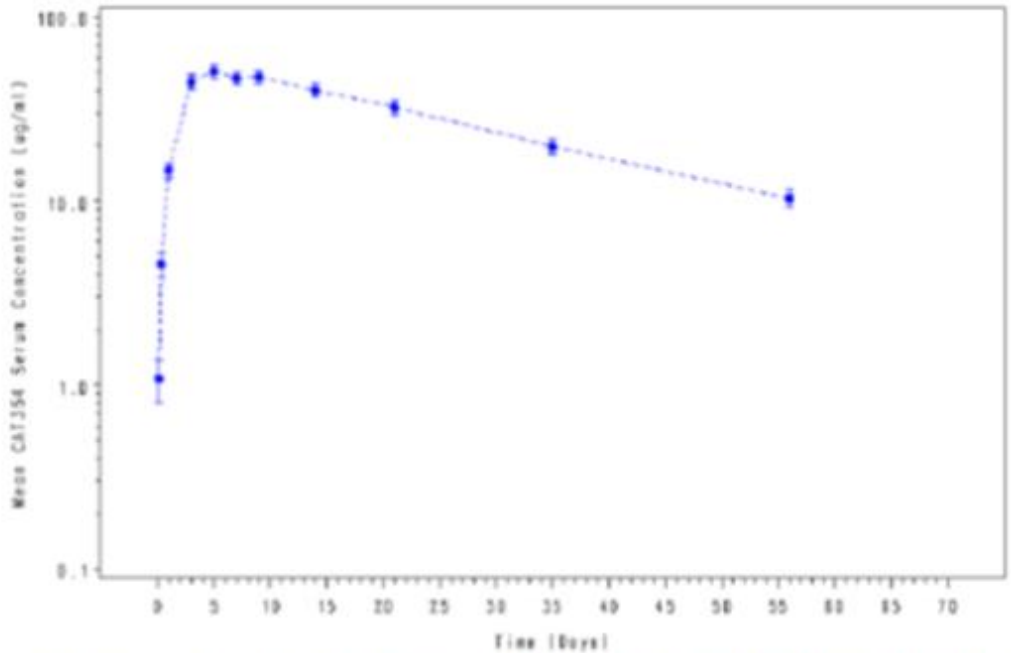
Results

20 subjects were dosed and completed the trial. All subjects were white and 70% were male. The median age was 14.5 years (mean: 14.2; SD: 1.8), the mean body weight was 61.3 kg (SD: 16.0, range: 40.2–93.5), and the mean BMI was 21.6 kg/m2 (SD: 4.1, range: 16.2–32.6).

Pharmacokinetics

The mean concentration-time profile for tralokinumab is shown in Panel 5, and key PK parameters are shown in Panel 6.

Panel 5 ***CD-RI-CAT-3541054 – mean serum concentrations of tralokinumab after a single subcutaneous dose (300 mg)***



Notes: Concentrations shown are arithmetic mean ± standard error of the mean; all 20 subjects were included in the analysis.

Abbreviations: CAT-354 = tralokinumab.

Panel 6 ***CD-RI-CAT-354-1054-pharmacokinetic parameters for tralokinumab after a single subcutaneous dose (300 mg)***

C_{max} (µg/mL)	t_{max} (days)	$AUC_{0-\infty}$ (µg×day/mL)	CL/F (mL/day/kg)	V/F (mL/kg)	$t_{½}$ (days)
50.8 ± 35.2%	5.2 (2.9, 9.1)	1697 ± 37.7%	3.1 ± 0.90	94.0 ± 21.6	21.7 ± 4.5

Notes: C_{max} and $AUC_{0-\infty}$ are given as geometric mean ± coefficient of variation (%), t_{max} is given as median (minimum, maximum), and other parameters are given as arithmetic mean ± standard deviation; all 20 subjects were included in the analysis.

Abbreviations: $AUC_{0-\infty}$ = area under the serum concentration–time curve from time zero extrapolated to infinity; C_{max} = maximum serum concentration; CL/F = apparent clearance; $t_{½}$ = terminal elimination half-life; t_{max} = time to reach C_{max}.

The PK data were presented for all 20 subjects as well as for the 2 age cohorts, which included 10 subjects aged 12-14 years and 10 subjects aged 15-17 years. The mean concentration-time profile was consistent across the 2 cohorts, with slightly higher systemic exposure (mean Cmax and AUC values) in the younger group. This was most likely related to a lower mean body weight in the younger group (55.8 vs 66.8 kg).

Table 1 ***Summary of Pharmacokinetic Parameters (PK Population)***

PK Parameter (unit)	Cohort 1 12-14 years N = 10	Cohort 2 15-17 years N = 10	Total N = 20
t_{max} (days)	5.2 (3.0-9.1)	6.1 (2.9-9.0)	5.2 (2.9-9.1)
C_{max} (µg/mL)	57.0 ± 21.7 (38.1%)	50.6 ± 16.2 (31.9%)	53.8 ± 18.9 (35.2%)
$AUC_{(0\text{-}inf)}$ (µg•day/mL)	1916.0 ± 806.3 (42.1%)	1721.1 ± 568.5 (33.0%)	1818.6 ± 686.3 (37.7%)
$AUC_{(0\text{-}t)}$ (µg•day/mL)	1561.4 ± 614.9 (39.4%)	1384.6 ± 421.6 (30.5%)	1473.0 ± 521.1 (35.4%)
$t_{1/2}$ (days)	21.4 ± 5.5 (25.6%)	22.1 ± 3.5 (15.9%)	21.7 ± 4.5 (20.7%)
CL/F (mL/day)	181.1 ± 68.1 (37.6%)	199.4 ± 91.8 (46.0%)	190.2 ± 79.2 (41.6%)
Normalized CL/F (mL/day/kg)	3.3 ± 1.0 (31.4%)	2.9 ± 0.7 (22.9%)	3.1 ± 0.9 (27.9%)
V_z/F (mL)	5399.0 ± 1937.1 (35.9%)	6038.0 ± 1824.2 (30.2%)	5718.5 ± 1860.4 (32.5%)
Normalized V_z/F (mL/kg)	98.0 ± 28.6 (29.2%)	90.0 ± 11.5 (12.8%)	94.0 ± 21.6 (23.0%)

AUC = area under the concentration time curve, $AUC_{(0\text{-infinity})}$ = area under the concentration-time curve from zero to infinity; $AUC_{(0\text{-}t)}$ = area under the concentration-time curve from zero to last measurable concentration, C_{max} = maximum concentration, CL/F = apparent systemic clearance, CV = coefficient of variation, max = maximum, min = minimum, PK = pharmacokinetics, SD = standard deviation; t_{max} = time of occurrence for maximum drug concentration, $t_{1/2}$ = terminal phase elimination half life, V_z/F = apparent volume of distribution after non-intravenous administration

Data are presented as following: all PK parameters are arithmetic mean ± SD (CV%) apart from t_{max} displayed as median (minimum, maximum).

Comparison between adolescents and adults

The geometric mean Cmax was 50.8 µg/mL (SD: 18.9, n=20) and the median tmax was 5 days (range: 3-9 days) after a single SC dose of tralokinumab 300 mg, similar to the corresponding values observed in healthy adult subjects (trial CAT-354-0703). The systemic exposure, as assessed by Cmax and AUC, was higher in the adolescents than in the adults, which is most likely related to the lower mean body weight in the adolescents. The other PK parameters in the adolescent population in CD-RI-CAT-354-1054 (Panel 6) were broadly similar to those in the adult population.

Immunogenicity

All post-dose samples were negative for ADA following administration of tralokinumab.

Population PK analysis

The previously developed population PK model for the initial MAA, based on data from 10 clinical studies in adult subjects, was updated to include data from adolescent subjects in ECZTRA 6 and CD-RI-CAT-354-1054.

Population PK modelling of tralokinumab was performed using a non-linear mixed effect modelling approach in NONMEM 7.4. The covariate model building was repeated for the updated analysis using an automated stepwise covariate modelling (SCM) approach. All covariates found to be statistically significant during the SCM approach were evaluated for clinical relevance based on the same criteria as those defined in the original analysis.

The following covariates considered for the analysis were demographic factors (age, sex, body weight, race, and ethnicity), disease status (healthy, asthma, or AD), disease severity (baseline EASI score), and trial-related factors (concentration of drug formulation and ECZTRA trials versus other ['non-ECZTRA'] trials). Age group (adolescent, adult) as a covariate on CL and V2 or F was also included evaluated.

The predictive performance of the final population PK model was evaluated by generation of goodness-of-fit diagnostic plots, visual predictive checks (VPCs), and statistical significance (objective function value).

No simulations with the final model were performed.

Results

The dataset for the updated population PK model was based on 2,857 subjects dosed with tralokinumab, of whom 296 were adolescents. Data exclusions were documented. Likelihood-based methods for handling BLQ values were not used because the number of samples BLQ was <10% of the total samples in the dataset.

The final popPK model was a 2-compartment model with first-order absorption and elimination. All PK parameters were estimated with high precision (RSE<20%). Inter-individual variability on CL and V2 was moderate (30.7% and 38.3%, respectively). The degree of shrinkage for IIV on CL and V2 was acceptable (7% and 29%, respectively).

During the stepwise covariate search, all covariates that were identified as statistically significant in the original adult model were also significant in the updated model. These were: body weight, age, baseline EASI score, eGFR, sex (female), race (Asian and BAA), ethnicity (Hispanic or Latino), dilution of dose, disease type (asthma), and non-ECZTRA trials. Of these, only body weight on clearance (CL and Q) and volume (V2 and V3), non-ECZTRA trials on CL and V2, and concentration of drug formulation on F and ka were deemed clinically relevant predictors of tralokinumab exposure, which was in line with the results for adults. However, as both non-ECZTRA trials and concentration of drug formulation are extrinsic factors related to the drug development process, these covariates do not have any relevance for the future clinical use of the tralokinumab 150 mg/mL solution.

Panel 7 shows the popPK parameter estimates of the final model.

Panel 7 ***Final model: Population PK parameter estimates***

Parameter	Unit	Estimate[a]	RSE (%)[b]	Shrinkage (%)
PK (pharmacokinetic) parameter				
k_a (absorption rate constant)	day^{-1}	0.179	4	-
V_2 (central volume of distribution)	L	2.67	6	-
CL (clearance)	L/day	0.149	5	-
V_3 (peripheral volume of distribution)	L	1.44	6	-
Q (inter-compartmental clearance)	L/day	0.156	7	-
F (bioavailability)	Unitless	0.756	5	-
σ additive	µg/mL	0.358	10	-
σ proportional	CV	0.211	1	-
IIV (inter-individual variability)[c]				
IIV on V_2	CV%	38.3	4	29
IIV on CL	CV%	30.7	2	7
IIV on V_2:CL	Corr.	0.58[d]	-	-
Covariate				
V_2 and V_3 ~ Weight	Unitless	0.791	3	-
CL and Q ~ Weight	Unitless	0.859	3	-
CL ~ non-ECZTRA trials	Unitless	0.331	6	-
V_2 ~ non-ECZTRA trials	Unitless	0.246	12	-
F ~ Dilution[e]	Unitless	0.351	18	-
k_a ~ Dilution[e]	Unitless	-0.516	9	-

[a] For continuous covariates, the population estimate is for example: $CL_{population} \times$ (covariate/median (covariate))^CL~ $THETA_{covariate}$. For categorical covariates, the estimated parameter in a given category is for example: $CL_{population} \times (1+ THETA_{covariate})$. (THETA = fixed effect).

[b] RSE (relative standard error) was obtained from the COVARIANCE option in NONMEM.

[c] IIV (inter-individual variability) was calculated as $\sqrt{(e^{\omega^2}-1)}$.

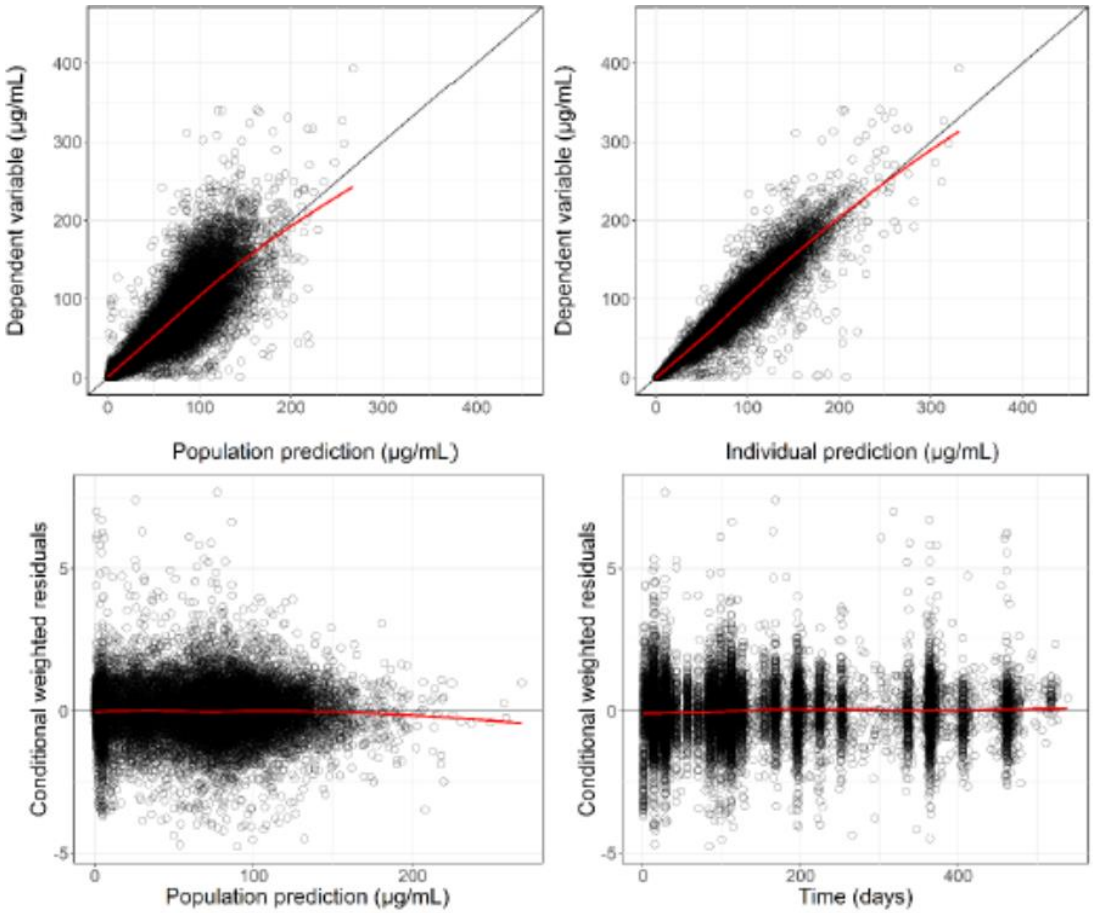
[d] Correlation was calculated as $\rho_{i,j} = \frac{\omega_{i,j}^2}{\omega_{i,i}*\omega_{j,j}}$.

[e] In the 45 mg dose group of trial D2213C00001, tralokinumab was diluted before subcutaneous administration. In all other trials with subcutaneous administration, tralokinumab was injected undiluted (see initial

Goodness of fit plots are provided in

Figure 1. The observed versus population- and individually predicted concentrations showed a random normal scatter around the identity, indicating no major systematic bias of the model. A similar trend was observed for the conditional weighted residuals versus population prediction. Finally, no time-dependent bias was observed for the conditional weighted residuals versus time, suggesting the absence of time-dependent PK.

Figure 1 ***Final model: Goodness-of-fit plots***



Top left: Correlation between the dependent variable (tralokinumab serum concentration) and the population predictions.

Top right: Correlation between the dependent variable (tralokinumab serum concentration) and the individual predictions.

Bottom left: Correlation between the conditional weighted residuals and the population predictions.

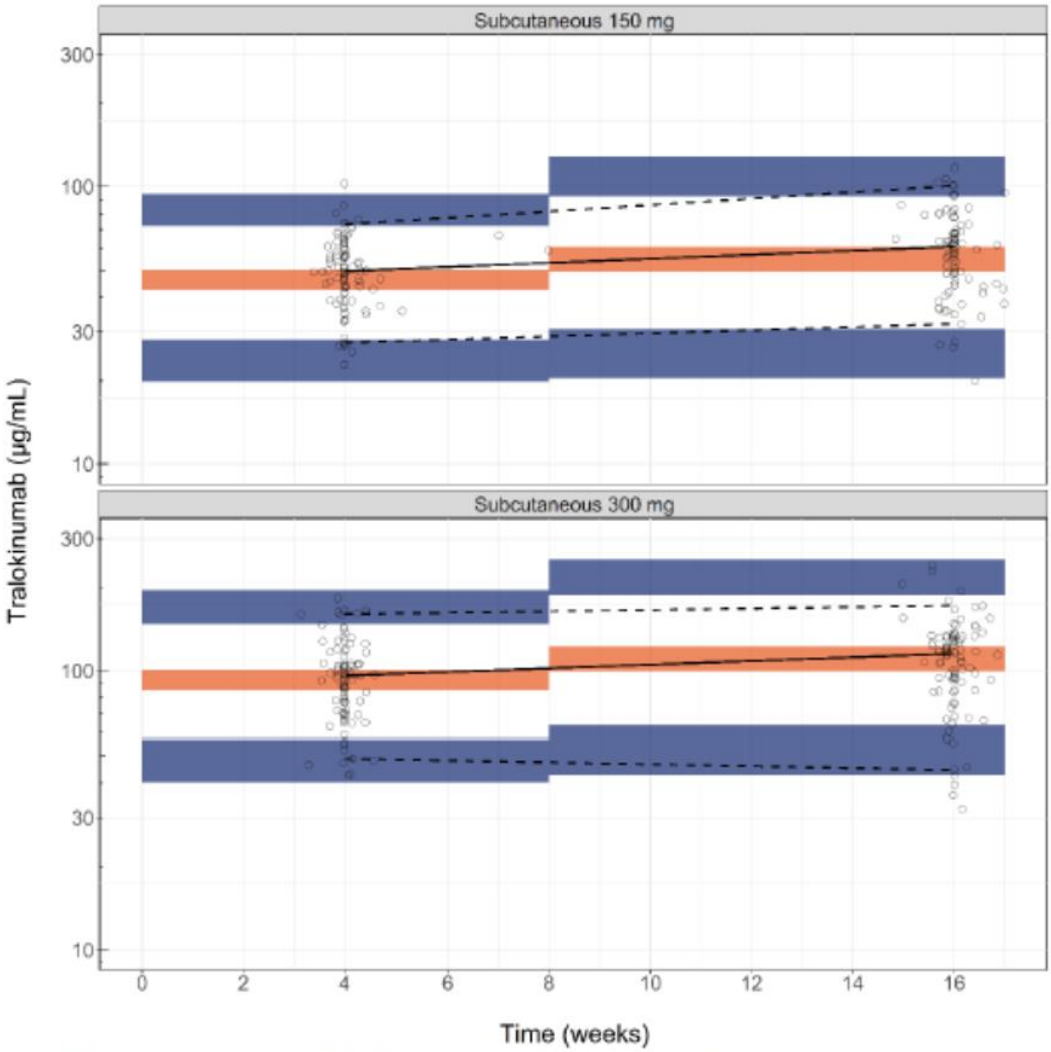
Bottom right: Correlation between the conditional weighted residuals and time.

The black circles represent the individual observations/predictions/conditional weighted residuals, and the red line is the trend line (LOESS).

VPCs were generated for the initial 16 weeks of treatment with tralokinumab 150 mg or 300 mg Q2W in adolescent subjects in the ECZTRA 6 trial. As apparent from the VPC of the serum concentration–time profile for ECZTRA 6 (

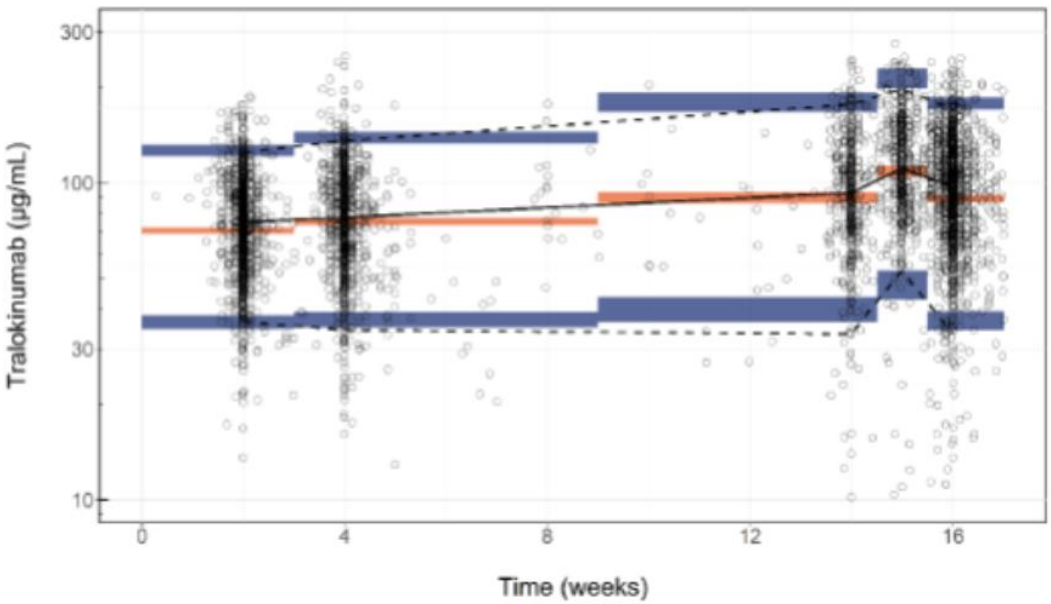
Panel 8), the final model provided an adequate description of the observed data, as the observed median was captured by the simulated median and in general the observed lower and upper percentiles were captured by the 95% CIs of the simulated upper and lower percentiles. A VPC was also generated for ECZTRA trials (Panel 9) excluding ECZTRA 6. The VPC provided an adequate description of the observed data, as the observed median as well the observed lower and upper percentiles were captured by the 95% CI of the simulated median and upper and lower percentiles.

Panel 8 ***Final model: Visual predictive check for Week 0-16 in ECZTRA 6 (adolescent subjects with AD)***



Notes: Visual predictive check (VPC) of the serum concentration–time profile of tralokinumab in adolescent subjects with atopic dermatitis following subcutaneous administration of tralokinumab 150 mg and 300 mg, depicting the observed concentration of tralokinumab (circles), the median of the observed concentration of tralokinumab (solid line), the 95% confidence interval of the simulated median (orange shaded area), the 95% confidence interval of the simulated lower 5th and the upper 95th percentiles (blue shaded areas), and the observed 5th and 95th percentile (dashed line). For visual purposes, serum concentrations below 10 µg/mL were excluded from the plot (not for the calculation of VPC statistics).

Panel 9 ***Final model: Visual predictive check for Week 0-16 in ECZTRA trials excluding ECZTRA 6***



Notes: Visual predictive check (VPC) of the serum concentration–time profile of tralokinumab in adolescent subjects with atopic dermatitis following subcutaneous administration of tralokinumab 150 mg and 300 mg, depicting the observed concentration of tralokinumab (circles), the median of the observed concentration of tralokinumab (solid line), the 95% confidence interval of the simulated median (orange shaded area), the 95% confidence interval of the simulated lower 5th and the upper 95th percentiles (blue shaded areas), and the observed 5th and 95th percentile (dashed line). For visual purposes, serum concentrations below 10 µg/mL were excluded from the plot (not for the calculation of VPC statistics).

2.3.3. Pharmacodynamics

ECZTRA 6 (LP0162-1334)

Sampling time points for PD assessments were as follows:

- In blood: serum biomarkers and whole blood mRNA biomarkers at Week 0 and 16; serum IgE at Week 0, 8, 16, 28, 52 and 66.
- In skin: skin tape strip samples for biomarkers of skin barrier function and skin inflammation at Week 0, 8 and 16; trans-epidermal water loss (TEWL) at Week 0 and 16; skin swabs for analysis of *Staphylococcus aureus* abundance and skin microbiome at Week 0 and 16.

Results

Serum biomarkers

The serum levels of the key AD disease biomarkers CCL17, IgE and IL-22 decreased in both tralokinumab dose groups relative to the levels in the placebo group during the initial treatment period. The reduction in all 3 biomarkers was of a clinically relevant magnitude, and no dose-dependent pattern was observed.

The concentration of CCL17 (TARC) was reduced by 0.50 NPX units during 16 weeks of treatment with tralokinumab 300 mg Q2W (Mann-Whitney-Wilcoxon test, $p<0.001$; Week 16 vs placebo) and by 0.55 NPX units during 16 weeks of treatment with tralokinumab 150 mg Q2W ($p<0.001$). In placebo-treated subjects, the level of CCL17 increased by 0.20 NPX units (median values).

The serum levels of IgE were reduced from 1768 IU/mL at baseline to 1565 IU/mL at Week 8 and 1472 IU/mL at Week 16 in subjects treated with tralokinumab 300 mg Q2W ($p<0.001$). In subjects treated with tralokinumab 150 mg Q2W, serum IgE levels were reduced from 2467 IU/mL at baseline to 1779 IU/mL at

Week 8 and 1550 IU/mL at Week 16 (p<0.001). Serum IgE levels in placebo-treated subjects increased from 1846 IU/mL to 2007 IU/mL at Week 8 and 2121 IU/mL at Week 16 (median values).

The serum levels of IL-22 were reduced from 17.8 mg/mL at baseline to 14.8 pg/mL at Week 16 (p=0.90) during 16 weeks of treatment with tralokinumab 300 mg Q2W and from 22.6 pg/mL at baseline to 18.1 pg/mL at Week 16 (p=0.52) in subjects treated with tralokinumab 150 mg Q2W. In placebo-treated subjects the IL-22 serum level was reduced from 34.3 pg/mL at baseline to 21.1 pg/mL at Week 16 (median values).

Comparison between adolescents and adults

The change from baseline up to Week 16 in serum levels of CCL17, IL-22, and IgE is shown for ECZTRA 6 and ECZTRA 1 in Panel 10. In ECZTRA 6, CCL17 and IL-22 were reduced to a lesser extent than in ECZTRA 1, whereas IgE was reduced to a similar extent.

Panel 10 ***Comparison of serum biomarkers in ECZTRA 6 and ECATRA 1: ratio of tralokinumab (150 mg or 300 mg) to placebo – relative change from baseline up to Week 16***

Serum biomarker	Relative change from baseline[a] to:	ECZTRA 6 (adolescents)		ECZTRA 1 (adults)
		150 mg Q2W (N=192)	300 mg Q2W (N=191)	300 mg Q2W (N=798)
CCL17	Week 16	0.66	0.94	0.42
IL-22	Week 16	0.90	0.74	0.54
IgE[b]	Week 8	0.66	0.81	0.87
	Week 16	0.55	0.72	0.66

Note: a = Values given as the ratio of tralokinumab to placebo, based on tralokinumab and placebo values given as the mean ratio to baseline ([mean Week 16/mean Week 0]$_{tralokinumab}$ / [mean Week 16/mean Week 0]$_{placebo}$) except for the IgE data – see note b; b = Ratio based on median values for tralokinumab and placebo.

Abbreviations: CCL17 = C-C motif chemokine ligand 17; IgE = immunoglobulin E; IL-22 = interleukin 22; N = number of subjects in the applicable tralokinumab dose group plus all subjects in the placebo group; Q2W = every 2 weeks.

Whole blood mRNA biomarkers

The effect of tralokinumab treatment on mRNA expression in whole blood samples was marginal with changes generally below 10% from baseline.

Biomarkers of skin barrier function in tape strip samples

At baseline, lesional skin had higher median levels of short-chain (C14-C18) and lower median levels of long-chain (C22-C32) ceramides and lysophosphatidylcholines compared with non-lesional skin. This is consistent with the expected shift in molecular species towards shorter-chain molecules in AD stratum corneum. Furthermore, the levels of natural moisturising factors (PCA, cis-UCA, and trans-UCA) were lower in lesional skin compared with non-lesional skin. Together, this indicates a reduced skin barrier integrity in lesional AD skin.

In both tralokinumab dose groups, the levels of short-chain lipids in lesional skin decreased from baseline to Week 16, and long-chain lipids increased, relative to the levels in the placebo group. Similarly, the level of natural moisturising factors (filaggrin metabolites) increased in both tralokinumab dose groups.

Although the analyses were based on a limited number of subjects (approximately 20–30 per treatment group) from selected trial sites, these data support a shift in stratum corneum lipid composition in lesional skin towards that of non-lesional skin following tralokinumab treatment.

Skin barrier function – Transepidermal water loss (selected trial sites)

The treatment effect was most pronounced in lesional skin compared to non-lesional skin, which was expected as the barrier integrity is higher in non-lesional skin and consequently the TEWL was about 50% lower in non-lesional skin compared to lesional skin at baseline. However, the low number of subjects (6

subjects in the tralokinumab 300 mg Q2W group, 4 in the tralokinumab 150 mg Q2W group, and 3 in the placebo group) and the large intra-individual variation in this assessment did not allow a meaningful statistical analysis between the groups.

Staphylococcus aureus abundance in skin

The absolute abundance of *S. aureus* at baseline was low in all 3 treatment groups (median levels <200 gene copies/cm^2 in lesional skin and <36 gene copies/cm^2 in non-lesional skin). In both tralokinumab dose groups, the median levels decreased markedly from baseline to Week 16 in both lesional and non-lesional skin.

In lesional skin the abundance of *S. aureus* was reduced from 166.2 to 1.1 gene copies/cm^2 (median values) during 16 weeks of treatment with tralokinumab 300 mg Q2W and from 144.4 to 1.1 gene copies/cm^2 in subjects treated with tralokinumab 150 mg Q2W. In subjects receiving placebo the *S. aureus* gene copy number was reduced from 200 to 38.4 gene copies/cm^2 from baseline to Week 16. The changes in the tralokinumab groups were not statistically different compared with placebo.

In non-lesional skin the abundance of *S. aureus* was reduced from 16.7 to 1.1 gene copies/cm^2 (median values) during 16 weeks of treatment with tralokinumab 300 mg Q2W and from 35.1 to 1.1 gene copies/cm^2 in subjects treated with tralokinumab 150 mg Q2W. In subjects receiving placebo the *S. aureus* gene copy number was not reduced (18.4 and 19.7 copies/cm^2 at baseline and Week 16, respectively). The changes in the tralokinumab groups were higher than for placebo (p=0.038 for tralokinumab 300 mg Q2W; p=0.001 for tralokinumab 150 mg Q2W).

Comparison between adolescents and adults

In ECZTRA 6, the absolute abundance of *S. aureus* in lesional skin at baseline was markedly lower than that observed in adult subjects in ECZTRA 1 (median of 166 gene copies/cm^2 in the tralokinumab 300 mg group in ECZTRA 6 vs 969 gene copies/cm^2 in ECZTRA 1). Although this difference could be due to differences in sample collection, it is possible that the level of *S. aureus* colonisation on the skin is lower in adolescent patients with AD than in adults.

In both tralokinumab dose groups, the median levels of *S. aureus* decreased markedly from baseline to Week 16 relative to the levels in the placebo group. At Week 16, the median levels in the tralokinumab groups were equal to the lower level of quantification, as more than half of the subjects were negative for *S. aureus* at this time point. This was most likely due to the low abundance levels at baseline, making it less meaningful to assess treatment effect based on the shift in *S. aureus* abundance, as was done in ECZTRA 1. Consequently, a quantitative comparison with the effect on *S. aureus* abundance in ECZTRA 1 was not possible.

Instead, the number of subjects with a quantifiable level of *S. aureus* at Week 16 was used as a measure of treatment effect. This analysis showed that approximately 40% of the subjects in the tralokinumab groups and 80% in the placebo group were positive for *S. aureus* at Week 16. This was comparable with the results observed in lesional skin for the phase 2b dose-finding trial in adults, D2213C00001, where the data were also presented as positive/negative but were based on an assessment of the number of bacterial colonies and not gene copy numbers.

2.3.4. Discussion on clinical pharmacology

The data included in this assessment were from 2 completed clinical trials in adolescent subjects. These data were also used in the population PK analysis. The same dose of tralokinumab in adults (300 mg Q2W) is proposed for adolescents with AD.

Pharmacokinetics

In the pivotal phase 3 study (ECZTRA 6) in adolescent subjects with moderate-to-severe AD, sparse PK sampling at trough was conducted. The results support dose linear PK of tralokinumab, which is consistent with the PK of tralokinumab observed in adult subjects. Trough concentrations at Week 4 were close to steady-state concentrations owing to the initial loading dose administered. Systemic exposure of tralokinumab was higher in adolescents than in adults for a given dose, which can be attributed to the lower mean body weight in the adolescents compared to adults.

Study CD-RI-CAT-354-1054 was the first study with tralokinumab in an adolescent population. Following a single 300 mg dose of tralokinumab, rich PK sampling was conducted. There was an adequate representation of the entire adolescent age range as evidenced by an equal number of subjects in the two cohorts (12 to 14 years and 15 to 17 years). Further, subject body weight, body height, and body mass index (BMI) at baseline were representative of the population of interest.

PK analysis showed that tralokinumab is slowly absorbed with a tmax ranging from 3 to 9 days post-dose and a mean terminal half-life of around 22 days, which is consistent with the results previously observed in adult subjects.

Population PK analysis

This update of the adult population PK model with data from adolescent subjects primarily focused on the covariate analysis and specifically if additional covariates should be included to predict tralokinumab exposure in adolescent subjects.

Overall, there are no major issues with this analysis. The methods used are acceptable. Data exclusions were well documented and acceptable. The structural model, based on the adult dataset, described the PK of tralokinumab in adolescent subjects adequately and the predictive performance of the final model was acceptable.

The covariate analysis, based on both statistical significance and clinical relevance criteria identified the same covariates as those identified in the previous analysis in adults. They were body weight, non-ECZTRA trials, and concentration of the drug formulation.

Immunogenicity

The immunogenicity results observed in ECZTRA 6 showed a treatment-emergent ADA incidence rate of 7.3% in tralokinumab-treated adolescent subjects. Numerically, this incidence rate in adolescents is slightly higher compared to the adult population in the ECZTRA trials (treatment-emergent ADA incidence 4.5%). However, a statistical comparison was not appropriate due to the low number of ADA-positive patients overall. The rate of nAb was comparably low in adolescent (0.7%) and adult subjects (1.0%). Further, there was no apparent impact of ADA on the PK, efficacy or safety of tralokinumab. Overall, it is agreed that the results suggest low immunogenic potential of tralokinumab in adolescent subjects.

Consistent with the results of ECZTRA 6, tralokinumab showed low immunogenic potential in Study CD-RI-CAT-354-1054, with no subjects having an ADA response following a single SC 300 mg dose.

Pharmacodynamics

In ECZTRA 6, the results of the PD assessment support the mechanism of action of tralokinumab and were generally consistent with those reported in adult subjects.

The serum levels of the key AD disease biomarkers CCL17, IL-22, and IgE were reduced at Week 16 in subjects receiving tralokinumab compared with subjects receiving placebo, supporting an anti-inflammatory effect of tralokinumab. The stratum corneum lipid composition in subjects receiving tralokinumab shifted from a typical AD lesional skin profile at baseline, indicating a disrupted skin barrier, towards a non-lesional profile at Week 16, suggesting improvement of the skin barrier function. *S. aureus* abundance in both lesional and non-lesional skin was strongly supressed at Week 16 in subjects receiving tralokinumab compared with subjects receiving placebo. Lipidomic and gene expression skin biomarker data indicate improved barrier integrity and better control of skin abnormalities for tralokinumab 300 mg Q2W than for tralokinumab 150 mg Q2W at Week 16.

2.3.5. Conclusions on clinical pharmacology

In terms of clinical pharmacology, no major objections were raised. Other concerns have been resolved.

The CHMP considered that the clinical pharmacology package was sufficient to support the following dosing recommendations in adolescent patients 12 years and older:

The recommended dose of tralokinumab for adult and adolescent patients 12 years and older is an initial dose of 600 mg (four 150 mg injections) followed by 300 mg (two 150 mg injections) administered every other week as subcutaneous injection.

2.4. Clinical efficacy

2.4.1. Dose response study

Dose regimens selected for evaluation in ECZTRA 6

The phase 2b dose-finding trial in adult subjects with moderate-to-severe AD evaluated 3 dose levels of 45, 150, and 300 mg tralokinumab Q2W+TCS. The difference to placebo increased with increasing dose of tralokinumab for most of the efficacy endpoints – including the primary endpoints (change from baseline in EASI at Week 12, and IGA 0/1 combined with at least a 2-grade reduction in IGA from baseline). Furthermore, the safety profile of tralokinumab 300 mg was acceptable. Therefore, tralokinumab 300 mg Q2W was chosen for the phase 3 development programme in adults.

In adolescents, a phase 1 trial with tralokinumab in subjects with asthma showed PK parameters that resembled those reported for the adult population when body weight was accounted for. It has been shown that the exposure of tralokinumab at steady state increases with decreasing body weight. However, this does not translate into a pronounced impact of body weight on the efficacy of tralokinumab. To establish an appropriate dose of tralokinumab in the adolescent population, both tralokinumab 150 mg and tralokinumab 300 mg were included in ECZTRA 6. For each dose, an initial treatment regimen of tralokinumab Q2W for 16 weeks was chosen, similar to what was done in the phase 3 trials in adults. From Week 16 onwards, a maintenance treatment regimen of Q4W was included for each dose, in addition to the Q2W maintenance regimen, to investigate whether less frequent dosing of tralokinumab is sufficient for long-term maintenance of efficacy in adolescents.

2.4.2. Main study

ECZTRA 6: randomised, double-blind, placebo-controlled, parallel-group, multi-centre trial to evaluate the efficacy, safety, and tolerability of

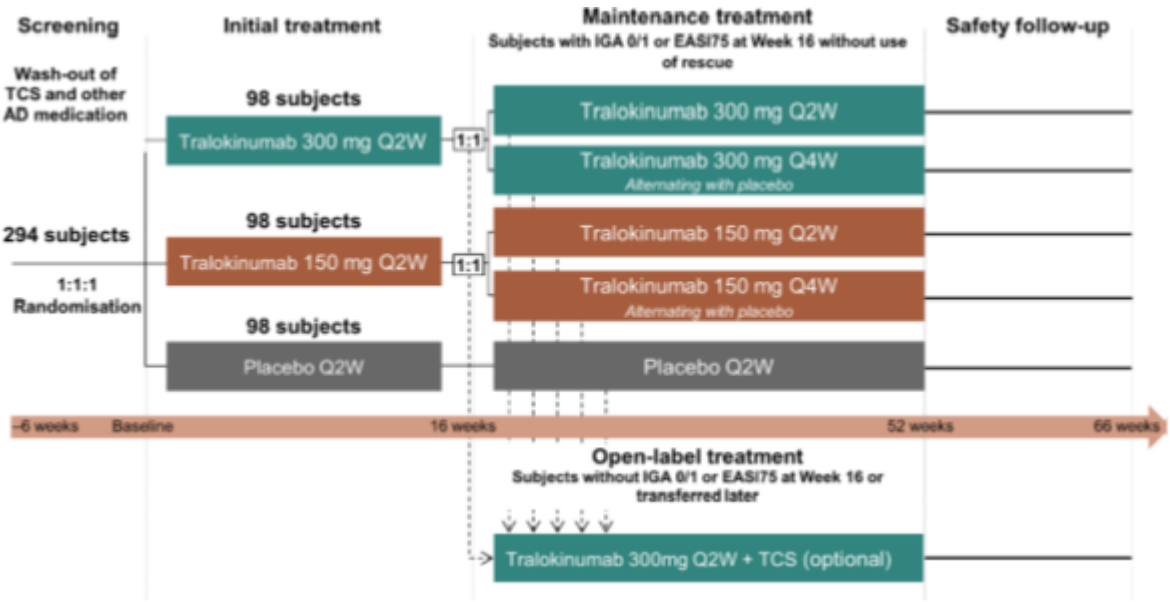
tralokinumab monotherapy in adolescent subjects with moderate-to-severe atopic dermatitis who are candidates for systemic therapy.

Methods

This was a phase 3 randomised, double-blind, placebo-controlled, parallel-group, multi-centre trial evaluating the efficacy, safety, and tolerability of tralokinumab monotherapy in adolescent subjects with moderate-to-severe atopic dermatitis who are candidates for systemic therapy.

The trial consisted of a screening period of 2 to 6 weeks, an initial treatment period of 16 weeks, a maintenance treatment period of 36 weeks in subjects who obtained a clinical response at Week 16, and an off-treatment follow-up period of 14 weeks for assessment of safety.

Panel 11 ***Trial design***



Trial periods

Screening period (Week -6 to Week 0)

The screening period had a minimum duration of 2 weeks and a maximum duration of 6 weeks and included 1 or 2 screening visits. The exact duration of the screening period depended on the wash-out period defined by the exclusion criteria. If no wash-out or only a 2-week wash-out was required, screening Visits 1 and 2 were combined (Week -2; Visit 2). Eligibility was assessed at the (first) screening visit and on Day 0 prior to randomisation.

All subjects were to use an emollient twice daily (or more, as needed) for at least 14 days before randomisation and were to continue this treatment throughout the trial.

Initial treatment period (Week 0 to Week 16)

Following the screening period, approximately 294 subjects were planned to be randomised 1:1:1 to one of the following groups stratified by region (Europe, North America, Australia, and Japan) and baseline disease severity (IGA of 3 or 4):

• Tralokinumab 300 mg Q2W: tralokinumab 600 mg (loading dose) at baseline, then tralokinumab 300 mg Q2W.

• Tralokinumab 150 mg Q2W: tralokinumab 300 mg (loading dose) at baseline, then tralokinumab 150 mg Q2W.

• Placebo Q2W: placebo (loading dose) at baseline, then placebo Q2W.

Maintenance treatment period (Week 16 to Week 52)

Subjects achieving the protocol-defined clinical response (defined as IGA of 0 or 1 [IGA 0/1] or at least 75% reduction in EASI score from baseline [EASI75]) at Week 16 without use of rescue medication from Week 2 to Week 16 continued into maintenance treatment until Week 52.

Subjects achieving a clinical response at Week 16 and who had been randomised to tralokinumab in the initial treatment period were re-randomised 1:1 to maintenance treatment regimens based on their initial treatment regimen and stratified by region and IGA response at Week 16 (IGA 0/1 or IGA >1).

Subjects who were initially randomised to tralokinumab 300 mg were re-randomised 1:1 to:

• Tralokinumab 300 mg Q2W.

• Tralokinumab 300 mg Q4W: alternating dose administrations of tralokinumab 300 mg or placebo.

Subjects who were initially randomised to tralokinumab 150 mg were re-randomised 1:1 to:

• Tralokinumab 150 mg Q2W.

• Tralokinumab 150 mg Q4W: alternating dose administrations of tralokinumab 150 mg or placebo.

Subjects 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 while maintaining blinding.

Open-label treatment period (Week 16 to Week 52)

Subjects who did not achieve the protocol-defined clinical response at Week 16 and subjects who received rescue treatment from Week 2 to Week 16 were transferred to open-label treatment (tralokinumab 300 mg Q2W with optional use of TCS and/or TCI) at Week 16, if considered appropriate by the investigator.

In addition, subjects were transferred from maintenance treatment to open-label treatment if they met any of the criteria listed below and transfer to open-label treatment was considered appropriate by the investigator.

Subjects with IGA=0 at Week 16:

• IGA of at least 2 and not achieving EASI75 over at least a 4-week period (i.e. over 3 consecutive visits).

Subjects with IGA=1 at Week 16:

• IGA of at least 3 and not achieving EASI75 over at least a 4-week period (i.e. over 3 consecutive visits).

Subjects with IGA >1 at Week 16:

Not achieving EASI75 over at least a 4-week period (i.e. over 3 consecutive visits).

Subjects who receive rescue treatment:

If rescue treatment was administered during the maintenance treatment period, subjects were transferred to open-label treatment. For subjects who received systemic rescue treatment, open-label treatment was not to be initiated sooner than 5 half-lives after the last dose of the systemic rescue treatment.

Subjects who were transferred to open-label treatment continued their scheduled visit sequence.

Safety follow-up period (Week 52 to Week 66)

After completion of the treatment periods or premature discontinuation of IMP, all subjects completed an off-treatment follow-up period for the assessment of safety, PK, and immunogenicity (i.e. ADA), except subjects who transferred to ECZTEND before Week 66 (see below). During follow-up, subjects were allowed to receive standard of AD care (excluding biologic therapies) at the investigator's discretion, if needed.

Long-term extension trial (ECZTEND)

Eligible subjects from selected countries (Belgium, Canada, France, Germany, Great Britain, Poland, and United States) were invited to enter a long-term extension trial conducted under a separate protocol (ECZTEND). Subjects who transferred to ECZTEND were required to have had their last visit in the treatment period (Week 52) under the current protocol (ECZTRA 6).

Subjects could enter ECZTEND with up to 26 weeks from their last IMP injection in the present trial (Week 50) to their first IMP injection in ECZTEND. Subjects could therefore enter ECZTEND without completing the safety follow-up visit (16 weeks after their last IMP injection) in the present trial; those subjects will have their safety follow-up visit in ECZTEND.

During the COVID-19 pandemic, subjects who were unable to attend their Week 52 visit at site, the visit could be partially conducted over the phone. Such subjects were allowed to transfer to ECZTEND.

Study participants

Main inclusion criteria:

- Signed and dated informed consent prior to any protocol-related procedures. Signed and dated informed consent had to be provided by the subject's legal representative(s) and by the subject (as applicable according to national laws or regulations).
- Age 12 to 17 years
- Body weight at baseline ⩾30.0 kg.
- Diagnosis of AD as defined by Hanifin and Rajka (1980) criteria for AD.
- History of AD for ⩾1 year.
- History of TCS (topical corticosteroid (Europe: Class 3 or higher; US: Class 4 or lower) and/or TCI treatment failure or subjects for whom these topical AD treatments are medically inadvisable.
- AD involvement of ⩾10% BSA at screening and baseline (Visit 3) according to component A of SCORAD.
- An EASI score of ⩾12 at screening and ⩾16 at baseline.
- An IGA score of ⩾3 at screening and at baseline, equivalent to moderate-to-severe AD.
- An Adolescent Pruritus NRS* average score of ⩾4 during the week prior to baseline.

* Adolescent Pruritus NRS at baseline was calculated from daily assessments of worst itch (Adolescent Pruritus NRS) during the 7 days immediately preceding randomisation (Day -6 to 0). A minimum of 4 Adolescent Pruritus NRS scores out of the 7 days was required to calculate the baseline average score. For subjects who did not have at least 4 scores reported during the 7 days immediately preceding the planned randomisation date, randomisation was postponed until this requirement was met, but without exceeding the 6 weeks' maximum duration of screening.

- Subjects had to have applied a stable dose of emollient twice daily (or more, as needed) for at least

14 days before randomisation.

Main exclusion criteria:

- Active dermatologic conditions that may confound the diagnosis of AD or would interfere with assessment of treatment, such as scabies, cutaneous lymphoma, or psoriasis.
- Known active allergic or irritant contact dermatitis that was likely to interfere with the assessment of severity of AD.
- Use of tanning beds or phototherapy (narrow band ultraviolet B [NBUVB], UVB, ultraviolet A1 [UVA1], PUVA), within 6 weeks prior to randomisation.
- Treatment with the following immunomodulatory medications or bleach baths within 4 weeks prior to randomisation:
    - Systemic immunosuppressive/immunomodulating drugs (e.g. methotrexate, cyclosporine, azathioprine, mycophenolate mofetil, Janus kinase inhibitors).
    - Systemic corticosteroid use (excludes topical, inhaled, or intranasal delivery).
    - 3 or more bleach baths during any week within the 4 weeks.
- Treatment with the following topical medications within 2 weeks prior to randomisation:
    - TCS.
    - TCI.
    - Topical PDE-4 inhibitor.
- Receipt of any marketed biological therapy or investigational biologic agents (including immunoglobulin, anti-IgE, or dupilumab):
    - Any cell-depleting agents including but not limited to rituximab: within 6 months prior to randomisation, or until lymphocyte count returned to normal, whichever was longer.
    - Other biologics: within 3 months or 5 half-lives, whichever was longer, prior to randomisation.
- Subjects who had received treatment with any non-marketed drug substance (that is, an agent which had not yet been made available for clinical use following registration) within 3 months or 5 half-lives, whichever was longer, prior to randomisation.
- Major surgery within 8 weeks prior to screening, or planned inpatient surgery, or hospitalisation during the trial period.
- Known or suspected hypersensitivity to any component of the IMP.
- History of any active skin infection within 1 week prior to randomisation.
- History of a clinically significant infection within 4 weeks prior to randomisation which, in the opinion of the investigator or sponsor's medical expert, might have compromised the safety of the subject in the trial, interfered with evaluation of the IMP, or reduced the subject's ability to participate in the trial. Clinically significant infections were defined as:
    - A systemic infection.
    - A serious skin infection requiring parenteral (intravenous or intramuscular) antibiotics, antiviral, or antifungal medication.
- A helminth parasitic infection within 6 months prior to the date informed consent was obtained that had not been treated with, or had failed to respond to, standard of care therapy.

- History of immune complex disease.
- History of cancer:
    - Subjects who had had basal cell carcinoma, localised squamous cell carcinoma of the skin, or in situ carcinoma of the cervix were eligible provided that the subject was in remission and curative therapy was completed at least 12 months prior to the date informed consent was obtained.
    - Subjects who had had other malignancies were eligible provided that the subject was in remission and curative therapy was completed at least 5 years prior to the date informed consent was obtained.
- Tuberculosis requiring treatment within the 12 months prior to screening. Evaluation was according to local guidelines as per local standard of care.
- History of any known primary immunodeficiency disorder including a positive human immunodeficiency virus (HIV) test at screening, or the subject was taking antiretroviral medications as determined by medical history and/or subject's verbal report.
- History of attempted suicide or at significant risk of suicide (either in the opinion of the investigator or defined as a "yes" to suicidal ideation questions no. 4 or 5 or answering "yes" to suicidal behaviour on the Columbia-Suicide Severity Rating Scale [C-SSRS] Screening version).
- Any disorder which was not stable and in the investigator's opinion could:
    - Affect the safety of the subject throughout the trial.
    - Influence the findings of the trial.
    - Impede the subject's ability to complete the trial.
- Examples include but were not limited to cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological, immunological, and psychiatric disorders and major physical impairment.
- Any abnormal finding which in the investigator's opinion might have:
    - Put the subject at risk because of their participation in the trial.
    - Influenced the results of the trial.
    - Influenced the subject's ability to complete the trial.
- The abnormal finding had to be clinically significant and observed during the screening period. Examples included abnormal findings in physical examination, vital signs, ECG, haematology, clinical chemistry, or urinalysis.
- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level ≥2.0 times the ULN at screening.
- Positive hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb), or hepatitis C virus antibody (anti-HCV) serology at screening. Subjects with positive HBsAb could be randomised provided they were hepatitis B vaccinated and had negative HBsAg and HBcAb.

Treatments

The first day of dosing was considered Day 0 (Visit 3, baseline). Each subject received 4 SC injections (each of 1 mL) to receive a loading dose of tralokinumab or placebo. At subsequent treatment visits in the trial, each subject received 2 SC injections (each of 1 mL).

In the **initial treatment period** subjects received either:

- Tralokinumab 300 mg Q2W: tralokinumab 600 mg (4 mL) at baseline, then tralokinumab 300 mg (2 mL) Q2W.
- Tralokinumab 150 mg Q2W: tralokinumab 300 mg (2 mL) + placebo (2 mL) at baseline, then tralokinumab 150 mg (1 mL) + placebo (1 mL) Q2W.
- Placebo Q2W: placebo (4 mL) at baseline, then placebo (2 mL) Q2W.

In the maintenance treatment starting from Week 16, subjects with a clinical response (achieved without use of rescue treatment from Week 2 to Week 16) continued to receive 2 SC injections (each of 1 mL) of maintenance treatment for up to Week 50:

- Subjects initially randomised to tralokinumab 300 mg Q2W:
  - Subjects re-randomised to tralokinumab 300 mg Q2W: tralokinumab 300 mg (2 mL).
  - Subjects re-randomised to tralokinumab 300 mg Q4W: alternating doses of 300 mg tralokinumab (2 mL) or placebo (2 mL).
- Subjects initially randomised to tralokinumab 150 mg Q2W:
  - Subjects re-randomised to tralokinumab 150 mg Q2W: tralokinumab 150 mg (1 mL) + placebo (1 mL).
  - Subjects re-randomised to tralokinumab 150 mg Q4W: alternating doses of tralokinumab 150 mg (1 mL) + placebo (1 mL) or placebo (2 mL).
- Placebo Q2W: placebo (2 mL).

Subjects who transferred to open-label treatment received tralokinumab 300 mg (2 mL) at each dosing visit.

The last administration of IMP occurred at Week 50. To ensure blinding, all treatment groups received the same number of injections at each visit; thus, the tralokinumab 150 mg group received both tralokinumab and placebo injections at all dosing visits.

IMP was administered by a qualified, unblinded HCP.

The injections were administered into the SC tissue of the upper arm, anterior thigh, or abdomen, separated by at least 3 cm. The injection site was recorded in the source documents at each treatment visit and recorded in the eCRF.

Prior and concomitant therapy

Background treatment (emollients)

All subjects were required to use an emollient twice daily (or more, as needed) for at least 14 days before randomisation. The background treatment preferably had to be an additive-free, basic bland emollient. Subjects were required to continue their background emollient treatment throughout the trial.

Concomitant medication and concurrent procedures

Any medication or vaccine that the subject received from 3 months prior to screening through safety follow-up (Week 66) was recorded in the subject's medical record and the eCRF along with details such as medication name, indication, start and stop date of administration (and whether the medication was ongoing), dosage information (including dose, unit, and frequency), and route of administration.

Concurrent surgical procedures and procedures related to AD treatment (e.g. phototherapy or bleach baths) were also recorded in the subject's medical record and the eCRF. The following details were recorded: procedure, condition, diagnosis, and start and stop date (and whether the procedure was ongoing).

Investigators could prescribe concomitant medications or treatments to provide adequate supportive care as deemed necessary, except for medications considered prohibited.

The following concomitant medications related to AD treatment were permitted from screening through safety follow-up (Week 66):

- Oral antibiotics, antiviral, or antifungal therapy for skin infections as appropriate.
- Stable doses of an emollient
- Oral antihistamines.

Prohibited medication and procedures

The following medications were prohibited from randomisation through Week 52:

- TCS of any WHO class (except for subjects in open-label treatment).
- TCI (except for subjects in open-label treatment).
- PDE-4 inhibitors.
- UVA or UVB, PUVA, other phototherapy, or tanning beds.
- 3 or more bleach baths per week.

The following medications were prohibited during the trial from randomisation through safety follow-up (Week 66) or until first IMP injection in the long-term extension trial (ECZTEND):

- Systemic corticosteroids (nasal, ophthalmic, and inhaled corticosteroids were allowed).
- Systemic treatment with an immunosuppressive/immunomodulating agent (e.g. cyclosporine, mycophenolate mofetil, azathioprine, methotrexate, Janus kinase inhibitors, interferon-gamma, dupilumab, or other biologics).

The sponsor's medical expert was to be notified if a subject received any of the following prohibited medications from randomisation through safety follow-up (Week 66):

- Investigational agents other than tralokinumab.
- Immunoglobulin or blood products.
- Allergen immunotherapy.
- Live (attenuated) vaccine.

The sponsor's medical expert was to determine whether IMP discontinuation was required.

Inactive/killed vaccinations (e.g. inactive influenza) were allowed if they were not administered within 5 days before/after any trial visit.

Any prohibited treatments used during the trial were recorded as concomitant medication.

Rescue treatment

Initial treatment period, maintenance treatment period, and safety follow-up period

If medically necessary (i.e. to control intolerable AD symptoms), rescue treatment for AD could be provided to trial subjects at the discretion of the investigator. For analysis of the primary estimand for the primary

endpoints, subjects who received rescue treatment from Week 2 to Week 16 were considered as non-responders, but they continued IMP treatment if the rescue treatment consisted of topical medications only.

When possible, investigators were instructed to limit the first step of rescue therapy to topical medications and escalate to systemic medications only for subjects who did not respond adequately after at least 14 days of topical treatment. TCS of any WHO class and TCI could be used as topical rescue treatment.

Systemic rescue treatment with corticosteroids or non-steroidal systemic immunosuppressive drugs (cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, etc.) required immediate discontinuation of IMP. After the treatment with these medications was completed, IMP could be resumed if deemed appropriate by the investigator and sponsor's medical expert, but no sooner than 5 half-lives after the last dose of the systemic rescue medication. Use of biological rescue treatment was disallowed for the entire trial duration.

Open-label tralokinumab arm only

From Week 16 through safety follow-up (Week 66), subjects could use mild to moderate strength TCS and/or TCI as needed on lesional skin at the investigator's discretion. Use of TCS and TCI was recorded as concomitant medication.

Objectives and Outcomes/endpoints

Objectives and endpoints

Objectives[a]	Endpoints[a]
Primary objective	Primary endpoints
To evaluate the efficacy of SC administration of tralokinumab compared with placebo in treating adolescent subjects (age 12 to <18 years) with moderate-to-severe AD.	• IGA score of 0 (clear) or 1 (almost clear) at Week 16. • EASI75 at Week 16.
Secondary objectives	Secondary endpoints
To evaluate the efficacy of tralokinumab on severity and extent of AD, itch, and health-related quality of life compared with placebo.	*Severity and extent of AD* • Change in SCORAD from baseline to Week 16. *Itch* • Reduction of Adolescent Worst Pruritus NRS (weekly average) of at least 4 from baseline to Week 16. *Health-related quality of life* • Change in CDLQI score from baseline to Week 16.
To investigate the safety, immunogenicity, and tolerability of SC administration of tralokinumab compared with placebo when used to treat adolescent subjects (age 12 to <18 years) with moderate-to-severe AD.	• Number of adverse events. • Presence of anti-drug antibodies (yes/no).
Maintenance objective	Maintenance endpoints
To evaluate maintenance of effect with continued tralokinumab dosing up to 52 weeks for subjects achieving clinical response at Week 16.	• IGA of 0/1 at Week 52 among subjects with IGA of 0/1 at Week 16 achieved without rescue treatment from Week 2 to Week 16, after initial randomisation to tralokinumab. • EASI75 at Week 52 among subjects with EASI75 at Week 16 achieved without rescue treatment from Week 2 to Week 16, after initial randomisation to tralokinumab.

[a]The trial included supplementary objectives, 'additional secondary endpoints', and 'other endpoints' not addressed in this synopsis.

Abbreviations: AD = atopic dermatitis; CDLQI = Children's Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EASI75 = at least 75% reduction in EASI score; IGA = Investigator's Global Assessment; NRS = numeric rating scale; SC = subcutaneous; SCORAD = Scoring Atopic Dermatitis.

Sample size

Assuming a screening failure rate of 25%, approximately 392 subjects were expected to be screened and approximately 294 subjects were planned to be randomised 1:1:1 to initial treatment (98 subjects to tralokinumab 300 mg, 98 subjects to tralokinumab 150 mg, and 98 subjects to placebo). The sample size was chosen to provide a sufficient power for demonstrating efficacy of tralokinumab vs. placebo for the primary endpoints.

Under the assumption that the IGA 0/1 response rates at Week 16 for the tralokinumab 300 mg dose and placebo are 30% and 10%, respectively, the power to detect a difference between tralokinumab 300 mg and placebo would be approximately 94% at a 2-sided 5.0% significance level.

Further, assuming corresponding response rates of 40% and 15% for EASI75 at Week 16 would imply a nominal power of approximately 98% to detect a difference between tralokinumab 300 mg and placebo for that endpoint.

The combined power for detecting a difference between tralokinumab 300 mg and placebo in both primary endpoints at a 5.0% significance level would then be at least 92%.

For the tralokinumab 150 mg dose, the accumulated power for subsequently rejecting the 2 hypotheses of no difference to placebo for the primary IGA 0/1 and EASI75 endpoints at a 2.5% significance level became approximately 84% and 80%, when using the same assumptions as for the tralokinumab 300 mg dose.

Randomisation

Eligible subjects were randomised to treatment with either tralokinumab 300 mg Q2W, tralokinumab 150 mg Q2W, or placebo Q2W in a 1:1:1 ratio in the initial treatment period. Subjects who were randomised to tralokinumab and achieved a clinical response at Week 16 were eligible to continue maintenance treatment and were re-randomised based on their treatment in the initial treatment period. Subjects initially randomised to tralokinumab 300 mg Q2W were re-randomised in a 1:1 ratio (tralokinumab 300 mg Q2W: tralokinumab 300 mg Q4W) while subjects initially randomised to tralokinumab 150 mg Q2W were re-randomised in a 1:1 ratio (tralokinumab 150 mg Q2W: tralokinumab 150 mg Q4W).

A central IRT system was used to control the randomisation, re-randomisation, and stratification factors (region and disease severity), along with IMP supply chain and expiry tracking. The assignment to maintenance or open-label treatment was based on the evaluation of clinical response by the investigator at Week 16. For 9 subjects, clinical response status at Week 16 was entered incorrectly and consequently, the IRT system assigned these subjects to incorrect treatment after Week 16 (2 subjects were assigned to maintenance treatment despite not achieving IGA 0/1 or EASI75 and 7 subjects were assigned to open-label treatment despite achieving IGA 0/1 or EASI75 without use of rescue medication).

The randomisation scheme (including treatment allocation for each subject) for the trial was provided by the applicant.

Blinding (masking)

This was a double-blinded trial in which tralokinumab and placebo were visually distinct from each other. Neither the subject nor any of the investigators or LEO Pharma A/S staff who were involved in the treatment or clinical evaluation and monitoring of the subjects were aware of the treatment received.

The packaging and labelling of the IMPs contained no evidence of their identity. IMP was packed in identical boxes with non-sequential kit numbers to ensure that unblinding did not occur during shipment and handling of the drug.

Since tralokinumab and placebo were visually distinct and not matched for viscosity, IMP was handled and administered by a qualified, unblinded HCP at the site who was not involved in the management of trial subjects and who did not perform any of the assessments. If needed, the unblinded HCP could perform the safety assessments (except assessment of AEs) for subjects in open-label treatment.

If treatment allocation for a subject became known to the investigator or other trial staff involved in the management of trial subjects, LEO Pharma A/S was to be notified immediately. There were 2 cases of unblinding or potential unblinding of LEO Pharma staff. After evaluation of the cases, they were not considered to have an impact on the integrity of trial results.

If an issue arose with the IMP (e.g. damaged kit or syringe that had been assigned to a subject prior to administration, or any other unexpected event with the kit or syringe [e.g. a malfunction during IMP administration]), the unblinded HCP at the site was to contact the CRA to determine whether any specific actions were required.

The trial site maintained a written plan detailing which staff members were blinded/unblended and the process of IMP administration used to maintain the blind.

Statistical methods

Statistical Analysis Plan

The SAP was finalised before unblinding of the trial, but after blind review of the data.

In addition, the Statistical Analysis Plan includes supplementary statistical analyses and aspects that are not present in the latest protocol amendment. Supplementary analyses introduced according to LEO response to FDA Advice letter dated 21-Sep-2018; Ref ID: 4324159:

1. A tipping point analysis introduced as a sensitivity analysis number 3 for the primary estimand ('composite') for the primary endpoints (IGA 0/1 and EASI75) and the secondary endpoint (reduction of Adolescent Pruritus NRS weekly average of at least 4 (yes/no)).

2. Analyses of a new tertiary estimand ('composite') for the continuous secondary confirmatory endpoints (change in SCORAD and change in CDLQI). Analyses apply non-responder imputation for subjects who received rescue medication. A tipping point sensitivity analysis is included.

Other supplementary analyses introduced for consistency:

3. The same analysis and tipping point sensitivity analysis as above implemented as a new tertiary ('composite') estimand for the two secondary additional endpoints 'Change from baseline to Week 16 in EASI score' and 'Change from baseline to Week 16 in Adolescent Pruritus NRS (weekly average)'

Analysis Populations

All subjects randomised to initial treatment who were exposed to IMP and who were not enrolled at the two sites with GCP non-compliance issues were included in the ***full analysis set*** and analysed for efficacy up to Week 16 (Visit 11).

Subjects from two sites (n=2 and n=7) were excluded from the FAS due to several GCP non-compliance issues.

A *per protocol analysis set* was used as an efficacy subset for the analysis of the primary endpoints at Week 16 (Visit 11), and analyses based on the per protocol analysis set were performed to support the results obtained for the full analysis set. The per protocol analysis set was defined by excluding subjects from the full analysis set for whom any of the following conditions applied:

- Provided no assessment of IGA or EASI following start of treatment.
- Were known to have taken the wrong IMP throughout the initial treatment period of the trial.
- Did not fulfil the inclusion criteria no. 4, 7, 8, and 9.

A *maintenance analysis set* was defined as all subjects who received tralokinumab in the initial treatment period and who were re-randomised to maintenance treatment. Subjects who were not re-randomised to maintenance treatment and subjects from the two sites with GCP non-compliance issues were excluded from the maintenance analysis set.

A *safety analysis set* was defined as all subjects randomised to initial treatment who were exposed to IMP and not being from the two sites with GCP non-compliance issues. Hence, the safety analysis set was identical to the full analysis set.

A *maintenance safety analysis set* was defined as all subjects who were assigned to the maintenance treatment period, not being from the two sites with GCP non-compliance issues, and received at least 1 dose of maintenance treatment.

An *open-label safety analysis set* was defined as all subjects (except those from the two sites with GCP non-compliance issues) who at any point in time entered the open-label period and received at least 1 dose of open-label treatment.

A *safety follow-up analysis set* was defined as subjects (except those from the two sites with GCP non-compliance issues) completing the treatment period for whom the date of last contact was after the date of exposure end (i.e. after the Week 52 visit) and subjects (except those from the two sites with GCP non-compliance issues) not completing the treatment period and for whom the date of last contact was after the date of permanent discontinuation of IMP.

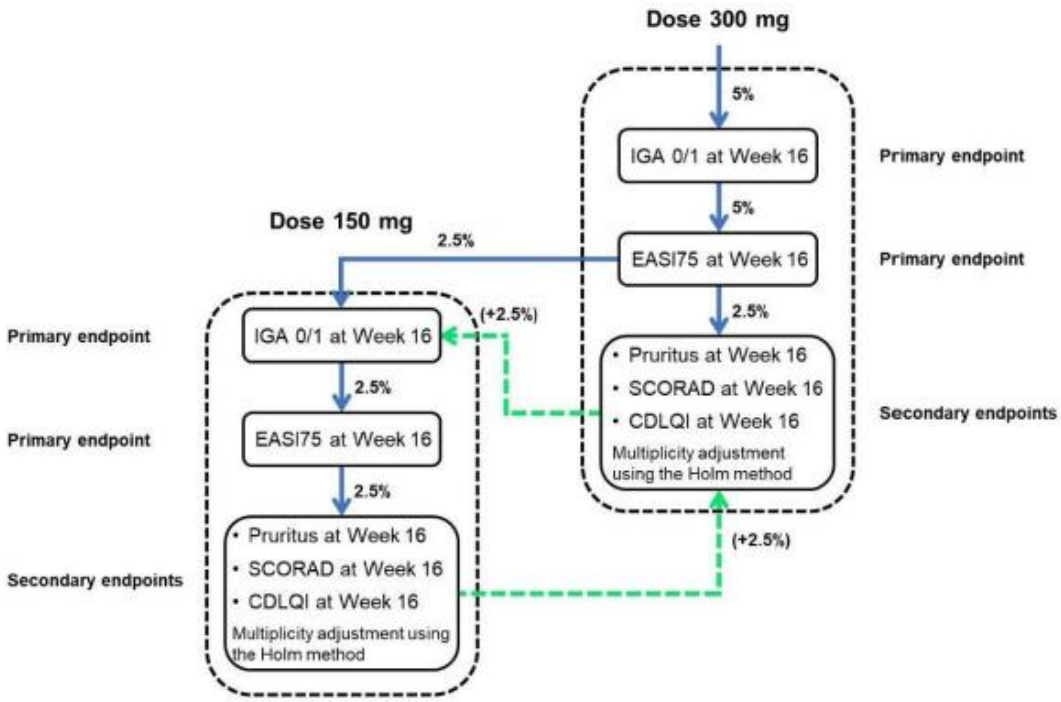
Multiplicity adjustments

The submission testing procedure was executed as follows:

IGA 0/1 at Week 16 between tralokinumab 300 mg and placebo was evaluated at a 5% significance level. If the test was statistically significant, EASI75 at Week 16 between tralokinumab 300 mg and placebo was evaluated at a 5% significance level. If both these tests were statistically significant, the significance level (alpha) was split evenly between the analyses of the 3 secondary endpoints at Week 16 between tralokinumab 300 mg and placebo and the analyses of IGA 0/1 at Week 16 between tralokinumab 150 mg and placebo, i.e. both were tested with alpha = 2.5%. If the test of IGA 0/1 at Week 16 for tralokinumab 150 mg was statistically significant, EASI75 at Week 16 between tralokinumab 150 mg and placebo was evaluated at a 2.5% significance level. If both tests of the primary endpoints for the 150 mg dose were statistically significant, the 3 secondary endpoints were evaluated at a 2.5% significance level. The evaluation of the 3 secondary endpoints at Week 16 between both doses of tralokinumab and placebo used the Holm-Bonferroni method for 3 ordered p-values at a 2.5% significance level to adjust for multiplicity.

If the tests were statistically significant for all 3 secondary endpoints for the 300 mg dose, the significance level could be passed on to testing of IGA 0/1 and all subsequent endpoints for the 150 mg dose. Likewise, if the test was statistically significant for all 3 secondary endpoints for the 150 mg dose, the significance level could be passed on for testing of the secondary endpoints for the 300 mg dose.

Figure 2 ***Testing procedure for the primary and secondary endpoints***



Analysis of primary endpoints

The primary endpoints were:

• IGA score of 0 (clear) or 1 (almost clear) at Week 16.

• EASI75 at Week 16.

All analyses of the primary endpoints were based on the full analysis set.

The following 3 estimands were defined for the primary endpoints:

• Primary estimand: 'composite'.

• Secondary estimand: 'hypothetical'.

• Tertiary estimand: 'treatment policy'.

The applied estimands incorporated 2 main types of intercurrent events that influenced how the treatment effects were estimated:

• **Initiation of rescue treatment**: some of the estimands used rescue treatment (from Week 2 to Week 16) as an event that modified the applied value of an endpoint, e.g. by defining a subject receiving rescue treatment as a non-responder.

• **Permanent discontinuation of IMP**: this event occurred when a subject was permanently withdrawn from the treatment or the trial. This could either happen at his/her own initiative or at the investigator's discretion. The event also included the possibility of a subject being lost to follow-up. The timing of the event was defined as the date of the early termination visit for withdrawn subjects or, in the case of a subject lost to follow-up, the date of the last known visit to the clinic. As for the rescue treatment, the event type was used to modify an applied endpoint value.

Panel 12 ***Overview of the estimand framework, imputation method, and statistical analyses at Week 16 – primary endpoints***

<table>
<tr><td colspan="2">All analyses:
The difference in response rates between the active tralokinumab arms and placebo were analysed separately for each of the tralokinumab dose groups using the Cochran-Mantel-Haenszel test (single imputation analyses) or using combined inference from multiple Mantel-Haenszel risk differences and associated standard errors using Rubin's rule (multiple imputation analyses).
Stratification factors:
Region (Europe, North America, Australia, and Japan) and baseline disease severity (IGA 3 or 4).</td></tr>
<tr><td colspan="2">Primary estimand 'composite':
Treatment difference in response rates of IGA 0/1 and EASI75 after 16 weeks achieved without rescue treatment from Week 2 to Week 16, regardless of treatment discontinuation.
The primary estimand assessed the expected difference in response rates at Week 16 (defined as response obtained without use of rescue treatment from Week 2 to Week 16), resulting from initiation of a treatment regimen with tralokinumab 300 mg or 150 mg compared to a treatment regimen with placebo.</td></tr>
<tr><td>Primary analysis</td><td>Subjects who received rescue treatment from Week 2 to Week 16 were considered non-responders.
Subjects with missing data at Week 16 and where rescue treatment had not been used prior to Week 16 were imputed as non-responders.</td></tr>
<tr><td>Sensitivity analysis 1</td><td>As primary analysis, with the exception that all subjects who permanently discontinued IMP prior to Week 16 were considered non-responders, even if no rescue treatment had been used.</td></tr>
<tr><td>Sensitivity analysis 2</td><td>As primary analysis, with the exception that missing data at Week 16 was imputed using LOCF rather than non-responder imputation for subjects who did not receive rescue treatment and did not withdraw due to an AE or lack of efficacy.</td></tr>
<tr><td>Sensitivity analysis 3</td><td>Tipping point analysis using multiple imputation:
Subjects who received rescue treatment from Week 2 to Week 16 were considered non-responders.
Missing Week 16 response was imputed from a Bernoulli distribution with varying parameter p for subjects in the placebo group who did not use rescue medication. Subjects in the tralokinumab groups with missing Week 16 data were imputed as non-responders.
Different percentages of placebo subjects were considered responders for the different values of p. The tipping point is the value of p which changed the conclusion from significant to non-significant.</td></tr>
<tr><td>Subgroup analysis</td><td>IGA 0/1 by baseline IGA and IGA 0/1 by region.
EASI75 by baseline IGA and EASI75 by region.</td></tr>
</table>

Supplementary analysis	Primary analysis of the primary estimand repeated based on the per protocol analysis set.
Secondary estimand 'hypothetical': Treatment difference in response rates of IGA 0/1 and EASI75 after 16 weeks if all subjects adhered to the treatment regimen in the sense that they did not discontinue IMP permanently and no rescue treatment was used from Week 2 to Week 16. *The secondary estimand assessed the expected difference in response rates achieved when adhering to the tralokinumab treatment regimen with no rescue treatment used from Week 2 to Week 16 as compared to a placebo treatment regimen with no rescue treatment in the same period.*	
Primary analysis	Data collected after permanent discontinuation of IMP or after use of rescue treatment from Week 2 to Week 16 was not included. Multiple imputation of missing values was applied within each treatment group, assuming data were missing at random. In the imputation model, the regions Asia, Australia, and Europe were pooled as data were sparse.
Sensitivity analysis	As primary analysis, except that imputation of missing values in the tralokinumab groups was based on regression models fitted on the observed data in the placebo group rather than the tralokinumab groups. In the imputation model, the regions Asia, Australia, and Europe were pooled as data were sparse.
Tertiary estimand 'treatment policy': Treatment difference in response rate after 16 weeks between tralokinumab and placebo regardless of rescue treatment and treatment discontinuation. *The tertiary estimand assessed the average difference in response rates, resulting from initiation of a treatment regimen with tralokinumab and additional rescue treatment as compared to a treatment regimen with placebo and additional rescue treatment.*	
Primary analysis	The primary analysis defined in the protocol could not be performed as insufficient data were available from subjects who discontinued IMP to support multiple imputation of missing values within the treatment groups.
Sensitivity analysis	All data were used as observed at Week 16. Missing values at Week 16 were imputed as non-responders.

Abbreviations: AE = adverse event; EASI = Eczema Area and Severity Index; EASI75 = at least 75% reduction

Analysis of secondary endpoints

The secondary endpoints were:

- Reduction of Adolescent Worst Pruritus NRS (weekly average) ≥4 from baseline to Week 16.
- Change in SCORAD from baseline to Week 16.
- Change in CDLQI score from baseline to Week 16.

All analyses of the secondary endpoints were based on the full analysis set. Reduction of Adolescent Worst Pruritus NRS weekly average of ≥4 was a binary endpoint and was analysed as described for the primary endpoint EASI75, using 3 estimands ('composite', 'hypothetical', and 'treatment policy').

For the 'treatment policy' estimand (tertiary estimand), the primary analysis was not conducted as insufficient data were available to support multiple imputation of missing values within the treatment

groups. However, the corresponding planned sensitivity analysis was conducted, analysing subjects with missing Week 16 data as non-responders, while otherwise using observed data for the remaining subjects.

Continuous secondary endpoints

The change from baseline to Week 16 in SCORAD and CDLQI were continuous endpoints.

An overview of the estimand framework for these endpoints is presented below.

Panel 13 ***Overview of the estimand framework, imputation method, and statistical analyses at Week 16 – continuous secondary endpoints***

Primary estimand 'hypothetical': Treatment difference in change from baseline to Week 16 in SCORAD and CDLQI, respectively, if all subjects adhered to the treatment regimen in the sense that they did not discontinue IMP permanently and no rescue treatment was used from Week 2 to Week 16. *The primary estimand assessed the expected benefit when adhering to the tralokinumab treatment regimen with no rescue treatment from Week 2 to Week 16 as compared to a placebo treatment regimen with no rescue treatment in the same period.*	
Primary analysis	Data collected after permanent discontinuation of IMP or after use of rescue treatment from Week 2 to Week 16 were not included in the analysis. Repeated measurements model on the post-baseline responses up to Week 16: Change in [SCORAD/CDLQI] = treatment × week + baseline [SCORAD/CDLQI] × week + region + baseline IGA. For subjects who did not have any post-baseline data collected before initiation of rescue medication, the Week 2 change was imputed as 0.
Sensitivity analysis	Data collected after permanent discontinuation of IMP or after use of rescue treatment were not included in the analysis. Multiple imputation of missing values was applied, based on regression models fitted on observed data from the placebo group and Asia, Australia and Europe regions pooled as data were sparse. ANCOVA model at Week 16: Change in [SCORAD/CDLQI] = treatment + baseline [SCORAD/CDLQI] + region + baseline IGA. Estimates and standard errors from analyses of multiple imputed datasets were combined using Rubin's rule.
Secondary estimand 'treatment policy': Treatment difference in change from baseline to Week 16 in SCORAD and CDLQI, respectively, between tralokinumab and placebo regardless of rescue treatment use and treatment discontinuation. *The secondary estimand assessed the average difference in change from baseline in SCORAD and CDLQI after 16 weeks, resulting from initiation of a treatment regimen with tralokinumab and additional rescue treatment as compared to a treatment regimen with placebo and additional rescue treatment.*	
Primary analysis	The primary analysis defined in the protocol could not be performed as insufficient data from subjects who discontinued IMP were available to support multiple imputation of missing values within the treatment groups.

Sensitivity analysis	All data were used as observed at Week 16. Multiple imputation of missing values for subjects who discontinued treatment before Week 16 was based on data from 3 subjects who discontinued treatment in the initial treatment period and had observed data at Week 16, disregarding treatment, region, and baseline characteristics. For subjects who did not discontinue treatment prior Week 16, missing data was imputed from subjects from the placebo arm who did not discontinue treatment prior to Week 16. ANCOVA model at Week 16: change in [SCORAD/CDLQI] = treatment + baseline [SCORAD/CDLQI] + region + baseline IGA. Estimates and standard error from analyses of multiple imputed datasets were combined using Rubin's rule.
Tertiary estimand 'composite': Treatment difference in change from baseline to Week 16 in SCORAD and CDLQI, respectively, achieved without use of rescue medication between Week 2 and Week 16, regardless of treatment discontinuation. *The tertiary estimand assessed the expected difference in change from baseline in SCORAD and CDLQI (defined as change at Week 16 obtained without use of rescue medication between Week 2 and Week 16), resulting from initiation of a treatment regimen with tralokinumab compared to a treatment regimen with placebo.*	
Primary analysis	Subjects who received rescue medication between Week 2 and Week 16 were considered non-responders by using worst observation carried forward (including the baseline value). Multiple imputation of missing values at Week 16 for subjects who did not use rescue medication between Week 2 and Week 16 was applied, assuming data were missing at random within treatment group. In the imputation model, the regions Asia, Australia, and Europe were pooled as data were sparse. ANCOVA model at Week 16: Change in [SCORAD/CDLQI] = treatment + baseline [SCORAD/CDLQI] + region + baseline IGA. Estimates and standard error from analyses of multiple imputed datasets were combined using Rubin's rule.
Sensitivity analysis	Tipping point analysis using multiple imputation. As primary analysis, except that varying values of Δ (Δ = 0 implies MAR) were added to the imputed values in the tralokinumab groups. The tipping point was then found as the value of Δ which changed the conclusion (of the primary analysis) from significant to non-significant.

Abbreviations: ANCOVA = analysis of covariance; CDLQI = Children's Dermatology Life Quality Index; IGA = Investigator's Global Assessment; IMP = investigational medicinal product; MAR = missing at random; SCORAD = Scoring Atopic Dermatitis.

Analysis of efficacy – maintenance treatment period

Maintenance endpoints

The 2 dichotomous maintenance endpoints were:

• IGA of 0/1 at Week 52 among subjects with IGA of 0/1 at Week 16 achieved without rescue treatment from Week 2 to Week 16, after initial randomisation to tralokinumab.

• EASI75 at Week 52 among subjects with EASI75 at Week 16 achieved without rescue treatment from Week 2 to Week 16, after initial randomisation to tralokinumab.

IGA of 0/1 and EASI75 at Week 52 were analysed using a binomial model, providing response rates and corresponding 95% confidence intervals based on the Wilson score method.

Only subjects who achieved IGA 0/1 or EASI75 at Week 16 without using rescue treatment from Week 2 to Week 16 were included in the analysis. All subjects who used rescue treatment (including TCS) between Week 16 and Week 52, permanently discontinued treatment, or transferred to open-label treatment were considered non-responders. Missing data for subjects who did not attend the Week 52 visit and who did not use rescue treatment between Week 16 and Week 52, were imputed as non-responders.

Continued treatment for non-IGA responders

The number of responders according to IGA 0/1 at Week 52 were tabulated for the subgroup of subjects in the maintenance analysis set who were re-randomised meeting the EASI75 criterion but not the IGA 0/1 criterion at Week 16. All subjects who prior to the Week 52 visit had received rescue treatment (including TCS), who were permanently discontinued from treatment, or who transferred to open-label treatment were considered non-responders in the analysis.

Analysis of efficacy – open-label treatment

To evaluate the efficacy in subjects who did not achieve IGA 0/1 or EASI75 at Week 16, IGA 0/1, EASI75, EASI50, EASI90, SCORAD75, and CDLQI reduction from baseline of at least 4 and 6, POEM reduction from baseline of at least 4 and 6, and Adolescent Worst Pruritus NRS reduction from baseline of at least 3 and 4, respectively, were summarised for the open-label period by visit, by initial treatment, and as a total, for previously tralokinumab-treated as a group and for both composite and treatment policy approach.

Results

Participant flow

Initial treatment period (Week 0 to Week 16)

A total of 347 subjects were screened for this trial. Of these, 46 subjects (13.3%) were screening failures. The remaining 301 subjects were randomised in a 1:1:1 ratio.

- 101 subjects randomised to tralokinumab 300 mg Q2W.
- 100 subjects randomised to tralokinumab 150 mg Q2W.
- 100 subjects randomised to placebo.

9 of the randomised subjects were enrolled at investigational sites with GCP non-compliance issues (3 subjects randomised to tralokinumab 300 mg Q2W, 1 subject randomised to tralokinumab 150 mg Q2W, and 5 subjects randomised to placebo). These subjects were excluded from the FAS. Furthermore, 1 subject in each treatment group was not dosed and therefore excluded from the FAS (2 subjects were randomised in error and therefore not dosed; 1 subject's parent withdrew consent prior to IMP administration).

Consequently, the FAS included:

- 97 subjects in the tralokinumab 300 mg Q2W group.

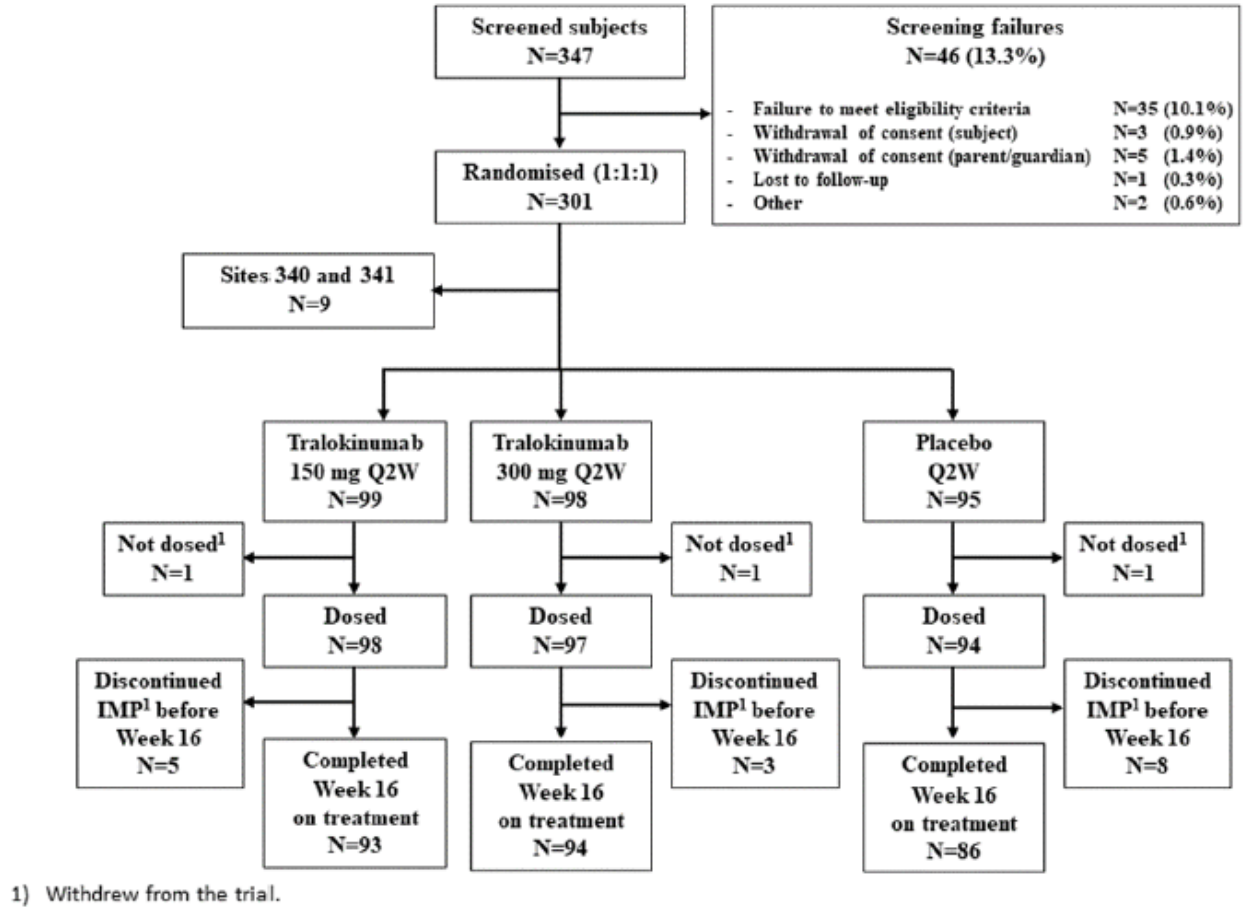
- 98 subjects in the tralokinumab 150 mg Q2W group.
- 94 subjects in the placebo group.

Of the randomised subjects, 3 subjects (3.0%) in the tralokinumab 300 mg Q2W group, 5 subjects (5.0%) in the tralokinumab 150 mg Q2W group, and 8 subjects (8.0%) in the placebo group permanently discontinued IMP before Week 16. The reasons for permanent discontinuation of IMP were:

- Adverse event (2 subjects [2.0%] in the tralokinumab 150 mg Q2W group).
- Lost to follow-up (2 subjects [2.0%] in the placebo group).
- Withdrawal by subject (2 subjects [2.0%] in the tralokinumab 150 mg Q2W group).
- Withdrawal by parent/guardian (2 subjects [2.0%] in the tralokinumab 300 mg Q2W group, 1 subject [1.0%] in the tralokinumab 150 mg Q2W group, and 3 subjects [3.0%] in the placebo group).
- Lack of efficacy (1 subject [1.0%] in the placebo group).
- Other (1 subject [1.0%] in the tralokinumab 300 mg Q2W group and 2 subjects [2.0%] in the placebo group).

In total, 273 subjects (90.7% of all randomised subjects) completed Week 16 on treatment. Of these 273 subjects, 94 subjects were treated with tralokinumab 300 mg Q2W, 93 subjects were treated with tralokinumab 150 mg Q2W, and 86 subjects received placebo.

Figure 3 ***Subject disposition, initial treatment period***



1) Withdrew from the trial.

Maintenance treatment period (Week 16 to Week 52)

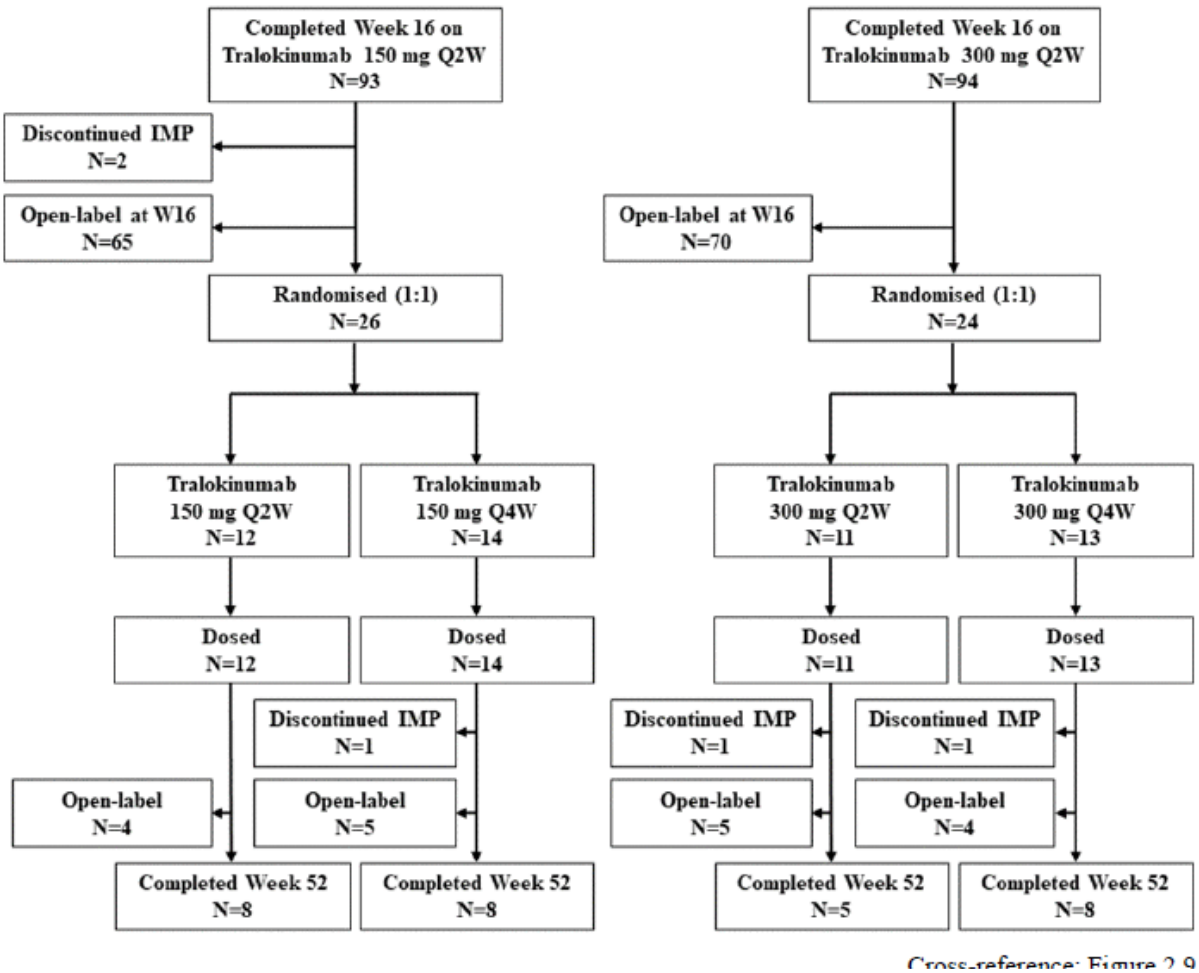
56 of the subjects in the FAS were assigned to maintenance treatment.

- 24 subjects initially randomised to tralokinumab 300 mg Q2W were re-randomised 1:1 to tralokinumab 300 mg Q2W or tralokinumab 300 mg Q4W.
- 26 subjects initially randomised to tralokinumab 150 mg Q2W were re-randomised 1:1 to tralokinumab 150 mg Q2W or tralokinumab 150 mg Q4W.
- 6 subjects initially randomised to placebo were assigned to continue placebo treatment.

None of the subjects in the FAS who were assigned to maintenance treatment had prior use of rescue medication and all these subjects were dosed with maintenance treatment.

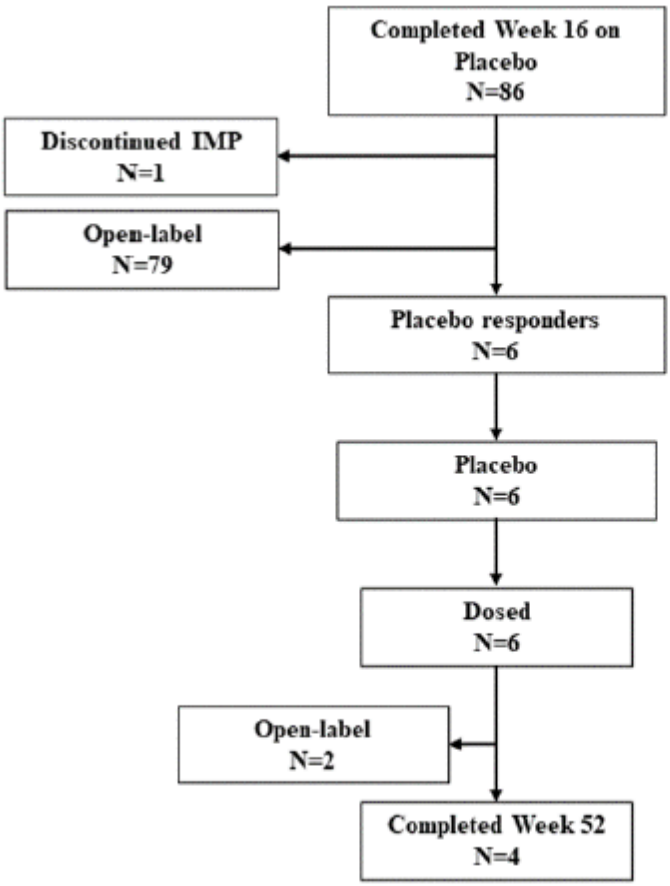
Amongst the 56 subjects in the FAS who were assigned to maintenance treatment, 3 subjects permanently discontinued IMP (1 subject in the tralokinumab 300 mg Q2W/Q2W group, 1 subject in the tralokinumab 300 mg Q2W/Q4W group, and 1 subject in the tralokinumab 150 mg Q2W/Q4W group).

Figure 4 ***Subject disposition, maintenance treatment period, subjects randomised to tralokinumab in maintenance analysis set***



Cross-reference: Figure 2.9

Figure 5 ***Subject disposition, maintenance treatment period, subjects assigned to placebo in maintenance treatment period***

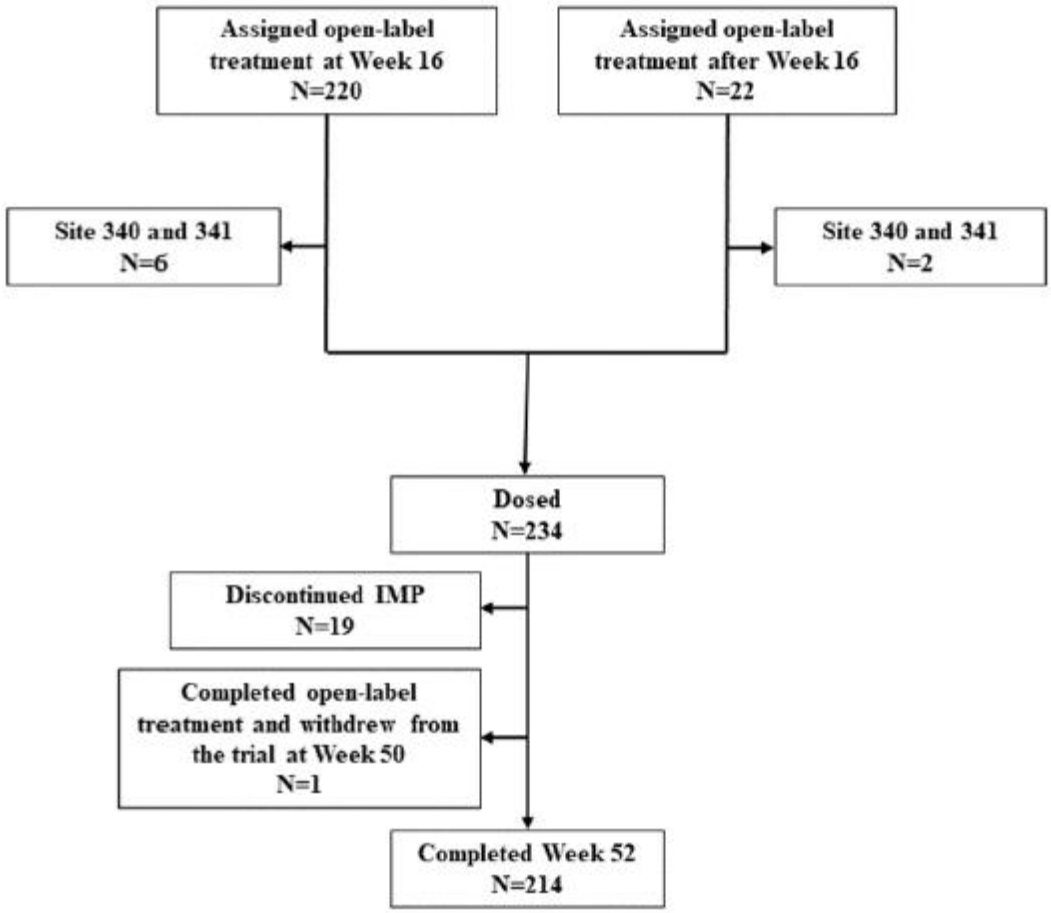


Open-label treatment period (Week 16 to Week 52)

A total of 220 subjects (214 subjects included in the FAS and 6 subjects randomised at investigational sites with GCP non-compliance issues) transferred to open-label treatment at Week 16.

Additionally, 22 subjects (20 subjects included in the FAS and 2 subjects randomised at investigational sites with GCP non-compliance issues) transferred to open-label treatment after Week 16.

Figure 6 ***Subject disposition, open-label treatment period, subjects in FAS assigned to open-label treatment***



Safety follow-up (off-treatment period) (Week 52 to Week 66)

Of the 289 subjects in the FAS, 152 subjects (52.6%) attended the safety follow-up visit. Reasons for not attending the safety follow-up visit included transferring to long-term extension for 96 subjects (33.2%), withdrawal by parent/guardian for 10 subjects (3.5%), lost to follow-up for 10 subjects (3.5%), withdrawal by subject for 9 subjects (3.1%), other for 6 subjects (2.1%), unknown for 4 subjects (1.4%), and AE for 2 subjects (0.7%).

Recruitment

Subjects were randomised at 72 sites across 10 countries (Australia, Belgium, Canada, France, Germany, Japan, the Netherlands, Poland, the UK, and the US).

Date of first subject first visit: 17-Jul-2018

Date of last subject last visit: 16-Mar-2021

Data lock point: 12-May-2021

Protocol amendments

There were 2 global substantial amendments, 3 global non-substantial amendments, and 1 country-specific non-substantial amendment to the original protocol dated 20-Mar-2018.

Panel 14 ***Protocol amendments – summary of changes***

Substantial global amendments
Amendment 2 **Issue date: 12-Jun-2018 (before FSFV)** • Extension of the post-IMP observation period at the first 3 visits in the initial treatment period in open-label treatment from 30 minutes to 2 hours.
Amendment 6 **Issue date: 06-Feb-2020 (after FSFV)** • Introduction of the possibility for eligible subjects in selected countries to continue in a long-term extension trial (ECZTEND). Subjects could enter ECZTEND from completion of the treatment period and up to 26 weeks from their last IMP injection in the present trial to the first IMP injection in ECZTEND. • Introduction of a database lock after the last subject had completed their final visit in the maintenance treatment period. The purpose of the introduced database lock was to ensure that LEO Pharma A/S will be able to fulfil the commitments in the PIP and PSP by making pharmacokinetic data available earlier for production of the pharmacokinetic model in adolescents that will inform the dose selection in subsequent paediatric trials. • Optimisation of the description of prohibited medication and procedures.
Non-substantial global amendments
Amendment 3 **Issue date: 21-Nov-2018 (after FSFV)** • Clarification of protocol sections describing skin swabs and transepidermal water loss assessments. • Update of requirements for IMP destructions at sites. • Introduction of an allowance for sites in Japan to change the order of trial procedures after randomisation to align with standard clinical procedures in Japan. • Inclusion of ClinicalTrials.gov identifier in the protocol. • Optimisation of the description of prohibited medication and procedures. • Adjustment of procedure for measuring vital signs to allow the measurements to be performed in either a supine or sitting position.
Amendment 4 **Issue date: 11-feb-2019 (after FSFV)** • Inclusion of 2 patient-reported outcomes (Patient Global Impression of Change and Adolescent Patient Global Impression of Severity) in the initial treatment period per request from the FDA. • Addition of footnotes to the schedules of trial procedures for the maintenance treatment period and open-label treatment to remind site staff that 2 hour post-IMP monitoring is required for the first 3 administrations of open-label tralokinumab. • Optimisation of the description of prohibited medication and procedures.

Amendment 5 **Issue date: 19-Jun-2019 (after FSFV)** • Introduction of a US-specific multiple testing procedure upon request from FDA. • Clarification that subjects in the open-label arm are allowed to use TCI as well as TCS. • Optimisation of the description of prohibited medication and procedures. • Change of the procedure of SAE reporting; SAEs were initially reported using paper forms but after this amendment SAEs were done in the eCRF (in Japan, SAE reporting continued to be done using paper forms).
Non-substantial country-specific amendments
Amendment 1 **Issue date: 01-May-2018 (before FSFV)** • Adjustment of the required qualifications of investigators in Japan to include both dermatologists and allergists.

Abbreviations: eCRF = electronic case report form; FDA = US Food and Drug Administration; FSFV = first subject first visit; IMP = investigational medicinal product; PIP = paediatric investigation plan; PSP = paediatric study plan; SAE = serious adverse event; TCI = topical calcineurin inhibitors; TCS = topical corticosteroid.

Changes to the conduct of the trial as a result of COVID-19

The onset of the global COVID-19 pandemic occurred after all subjects had passed their Week 16 visit in the trial. An urgent safety measure was implemented during the trial, which allowed for collection of adverse events by phone if site visits were not possible due to local preventive measures during the COVID-19 pandemic.

Protocol deviations:

No protocol deviations were assessed to have had any direct impact on subject safety. 8 protocol deviations related to violation of inclusion criterion no. 10 (an Adolescent Pruritus NRS average score of ≥4 during the week prior to baseline) were considered to have a critical impact on the efficacy analysis as randomisation of subjects without a baseline Adolescent Worst Pruritus NRS (weekly average) ≥4 reduced the size of the evaluable population for the reduction of Adolescent Worst Pruritus NRS (weekly average) ≥4 from baseline to Week 16 (confirmatory secondary endpoint; see the SAP). As subjects violating inclusion criterion no. 10 were excluded from the analyses of the reduction of Adolescent Worst Pruritus NRS ≥4 (confirmatory secondary endpoint), these protocol deviations did not affect the estimates for the reduction of Adolescent Worst Pruritus NRS (weekly average) ≥4 from baseline to Week 16. In addition, violations of inclusion criterion no. 10 were assessed not to have an impact on other efficacy analyses as subjects violating inclusion criterion no. 10 fulfilled key inclusion criteria no. 4, 7, 8, and 9.

A total of 377 major protocol deviations were reported during the trial, including the **8 critical protocol** deviations mentioned above. No major protocol deviations were reported at trial level or at country level. 18 major protocol deviations were reported at site level, of which 5 major site-level protocol deviations were reported at investigational site 340. 359 major protocol deviations were reported at subject-level, of which 36 protocol deviations were reported at two investigational sites.

Of the 359 major protocol deviations reported at subject-level, 37 protocol deviations resulted from the COVID-19 pandemic.

2 of the major site-level protocol deviations were considered critical:

- 1 major site-level protocol deviation reported at investigational site 340 was related to inadequate

temperature monitoring of IMP storage. The inadequate temperature monitoring at site 340 was documented in a temperature deviation report, and the sponsor IMP quality specialist assessed the issue as critical as the integrity of the IMP dispensed to subjects could have been impacted. However, the related site-level protocol deviation was not considered to have impacted the integrity of trial results as subjects from investigational site 340 were excluded from the full analysis set, and was not considered by the medical expert and global safety representative to have had a critical impact on subject safety as no AEs were reported at the site that could have been related to administration of IMP stored at incorrect temperatures.

- 1 major site-level protocol deviation concerned inadvertent circulation of unblinding information via email. Since the incident occurred 8 months after the subject had completed the initial blinded treatment period and transferred to open-label treatment, collection of blinded data in the initial treatment period for this subject was unaffected by the revelation of treatment allocation for the subject to the data manager and the CRA. Therefore, the incident was not considered to have impacted the scientific integrity of the results from the trial and thus the subject was not excluded from the full analysis set.

As mentioned above, no protocol deviations were considered to have had a direct impact on subject safety. 8 major subject-level protocol deviations related to violation of inclusion criterion no. 10 were considered critical, these protocol deviations were reported for 1 subject in the tralokinumab 300 mg Q2W group, 3 subjects in the tralokinumab 150 mg Q2W group, and 4 subjects in the placebo group.

As subjects violating inclusion criterion no. 10 were excluded from the analyses of the reduction of Adolescent Worst Pruritus NRS ≥4, these protocol deviations did not affect the estimates for the reduction of Adolescent Worst Pruritus NRS (weekly average) ≥4 from baseline to Week 16.

Panel 15 ***Major subject-level protocol deviations by country: screened subjects (excluding two investigational sites****)*

	Inclusion/ exclusion/ randomisation criteria		Informed consent (ICF)		Trial product		Assessments - safety/efficacy		Trial procedures		Other		Total	
	n	PD	n	PD	n	PD	n	PD	n	PD	n	PD	n	PD
All (N=338)	28	30	22	24	18	19	133	197	39	46	6	7	175	323
United States (N=123)	10	10	1	1	6	7	46	66	13	13	3	3	54	100
Australia (N=16)	1	1	3	3	1	1	6	9	2	3			9	17
Canada (N=57)	4	4	6	8	4	4	29	47	7	10	1	1	37	74
Great Britain (N=4)					2	2	4	9	1	1			4	12
Poland (N=57)	6	6	8	8	3	3	17	20	3	3			28	40
Belgium (N=8)	1	1					5	8					5	9
Germany (N=12)							5	9	3	5	2	3	6	17
France (N=10)	1	1	1	1	2	2	6	11	2	2			7	17
Japan (N=38)	3	3					9	9	3	3			13	15
Netherlands (N=13)	2	4	3	3			6	9	5	6			12	22

Abbreviations: ICF = informed consent form; n = number of subjects with protocol deviations; N = number of screened subjects; PD = number of protocol

Protocol deviation – Inclusion/Exclusion/Randomisation

39 major subject-level protocol deviations were related to inclusion/exclusion/randomisation criteria, of which 9 protocol deviations were reported at investigational site 340. Of these, 17 protocol deviations (7 from investigational site 340) were related to violation of inclusion criteria and 21 protocol deviations (2 from investigational site 340) were related to violation of exclusion criteria.

Protocol deviation – Informed consent

2 major site-level protocol deviations and 28 major subject-level protocol deviations were related to violation of various informed consent and assent procedures, of which 4 subject-level protocol deviations were reported at investigational site 340.

Protocol deviation – Late SAE reporting

3 major subject-level protocol deviations were related to late SAE reporting. These protocol deviations were not considered critical as the late SAE reporting did not have any impact on subject safety and did not lead to any delayed action in the trial.

Protocol deviation – Trial product

7 major site-level protocol deviations and 20 major subject-level protocol deviations were related to trial product, of which 1 major site-level protocol deviation and 1 major subject-level protocol deviation were reported at investigational site 340. Of the 20 major subject-level protocol deviations related to trial product, 1 protocol deviation, related to administration of IMP by unauthorised staff, resulted from the COVID-19 pandemic.

Protocol deviation – Assessments safety/efficacy

3 major site-level protocol deviations and 213 major subject-level protocol deviations were related to efficacy and safety assessments, of which 16 major subject-level protocol deviations were reported at investigational sites with GCP non-compliance issues. Of the 213 major subject-level protocol deviations related to efficacy and safety assessments, 27 protocol deviations resulted from the COVID-19 pandemic.

With the exception of the 3 protocol deviations for late SAE reporting described above, protocol deviations in this category were related to improperly performed assessments, missing assessments or sample acquisitions, assessments performed by unauthorised or unqualified staff, visits out of window or partially performed as a result of the COVID-19 pandemic, and use of prohibited medication.

Protocol deviation – Trial procedures

1 major site-level protocol deviation and 49 major subject-level protocol deviations were related to trial procedures, of which the site-level protocol deviation and 3 subject-level protocol deviations were reported at investigational sites with GCP non-compliance issues. Of the 49 major subject-level protocol deviations related to trial procedures, 9 protocol deviations, all related to visits performed out of window, resulted from the COVID-19 pandemic.

Protocol deviation – Other

5 major site-level protocol deviations and 10 major subject-level protocol deviations were reported in the category 'Other'.

Baseline data

Initial treatment period (Week 0 to Week 16)

Demographics

The demographics were well balanced between treatment groups in the initial treatment period. Minor differences in sex and race distribution were observed between treatment groups, however these are not considered to have had an impact on the interpretation of the results.

Panel 16 ***Demographics: full analysis set***

	Total (n=289)		Tralokinumab 150 mg Q2W (n=98)		Tralokinumab 300 mg Q2W (n=97)		Placebo (n=94)	
Age (years)								
N	289		98		97		94	
Mean (SD)	14.6 (1.7)		14.8 (1.7)		14.6 (1.7)		14.3 (1.6)	
Median	15.0		15.0		15.0		14.0	
Q1;Q3	(13.0;16.0)		(13.0;16.0)		(13.0;16.0)		(13.0;16.0)	
Min;max	12;17		12;17		12;17		12;17	
Sex, N (%)								
N (%)	289	(100.0)	98	(100.0)	97	(100.0)	94	(100.0)
Male	149	(51.6)	51	(52.0)	47	(48.5)	51	(54.3)
Female	140	(48.4)	47	(48.0)	50	(51.5)	43	(45.7)
Race, N (%)								
N (%)	289	(100.0)	98	(100.0)	97	(100.0)	94	(100.0)
White	164	(56.7)	55	(56.1)	56	(57.7)	53	(56.4)
Black or African American	32	(11.1)	7	(7.1)	14	(14.4)	11	(11.7)
Asian	71	(24.6)	28	(28.6)	20	(20.6)	23	(24.5)
American Indian or Alaska Native	3	(1.0)	2	(2.0)			1	(1.1)
Native Hawaiian or Other Pacific Islander	4	(1.4)			2	(2.1)	2	(2.1)
Other	15	(5.2)	6	(6.1)	5	(5.2)	4	(4.3)
Region, N (%)								
N (%)	289	(100.0)	98	(100.0)	97	(100.0)	94	(100.0)
North America	145	(50.2)	50	(51.0)	48	(49.5)	47	(50.0)
Europe	98	(33.9)	33	(33.7)	33	(34.0)	32	(34.0)
Australia	14	(4.8)	5	(5.1)	5	(5.2)	4	(4.3)
Asia	32	(11.1)	10	(10.2)	11	(11.3)	11	(11.7)

n: Number of subjects in analysis set. N: Number of subjects with observation. SD: Standard deviation. Q1: 1st quartile. Q3: 3rd quartile. %: Percentage of subjects. Q2W: Every 2 weeks.

There were no clinically relevant differences in height, weight, BMI, or vital signs (blood pressure, pulse, and temperature) at baseline between treatment groups in the initial treatment period.

Baseline disease severity

Apart from a higher percentage of subjects with severe disease in the tralokinumab 300 mg Q2W group (49.5%) compared with the tralokinumab 150 mg Q2W (44.9%) and placebo (45.7%) groups, the baseline disease severity was well balanced between treatment groups in the initial treatment period.

Panel 17 ***Baseline BSA, age of onset of AD and duration of AD: full analysis set***

	Total (n=289)	Tralokinumab 150 mg Q2W (n=98)	Tralokinumab 300 mg Q2W (n=97)	Placebo (n=94)
Baseline BSA (%)				
N	289	98	97	94
Mean (SD)	51.1 (23.2)	52.4 (22.6)	49.6 (23.3)	51.4 (23.9)
Median	49.0	49.0	44.0	52.0
Q1;Q3	(32.0;67.0)	(37.0;65.0)	(30.0;66.0)	(31.0;68.0)
Min;max	10;100	11;100	16;100	10;100
Age at onset of AD (years)				
N	289	98	97	94
Mean (SD)	2.3 (3.5)	2.1 (3.3)	2.5 (3.6)	2.3 (3.5)
Median	1.0	1.0	1.0	1.0
Q1;Q3	(0.0;3.0)	(0.0;3.0)	(0.0;3.0)	(0.0;3.0)
Min;max	0;16	0;14	0;14	0;16
Duration of AD (years)				
N	289	98	97	94
Mean (SD)	12.3 (3.6)	12.7 (3.7)	12.1 (3.7)	12.1 (3.5)
Median	13.0	13.0	13.0	13.0
Q1;Q3	(11.0;15.0)	(11.0;16.0)	(11.0;15.0)	(11.0;15.0)
Min;max	1;17	2;17	1;17	1;17

n: Number of subjects in analysis set. N: Number of subjects with observation. SD: Standard deviation. Q1: 1st quartile. Q3: 3rd quartile. Q2W: Every 2 weeks. BSA: Body surface area. AD: Atopic Dermatitis.

Panel 18 ***IGA, EASI, SCORAD, CDLQI, and Adolescent Worst Pruritus NRS (weekly average) at baseline: full analysis set***

	Total (n=289)	Tralokinumab 150 mg Q2W (n=98)	Tralokinumab 300 mg Q2W (n=97)	Placebo (n=94)
Investigator's Global Assessment, N (%)				
N (%)	289 (100.0)	98 (100.0)	97 (100.0)	94 (100.0)
Moderate Disease	154 (53.3)	54 (55.1)	49 (50.5)	51 (54.3)
Severe Disease	135 (46.7)	44 (44.9)	48 (49.5)	43 (45.7)
EASI Score				
N	289	98	97	94
Mean (SD)	31.68 (13.73)	32.05 (12.94)	31.76 (13.91)	31.21 (14.47)
Median	28.00	28.90	28.00	27.15
Q1;Q3	(21.10;38.10)	(21.40;39.40)	(21.05;37.80)	(19.70;35.80)
Min;max	16.0;72.0	16.0;68.4	16.0;72.0	16.0;68.4
SCORAD Score				
N	289	98	97	94
Mean (SD)	67.78 (14.29)	67.66 (14.38)	68.31 (13.71)	67.36 (14.91)
Median	66.90	65.00	68.30	66.65
Q1;Q3	(58.10;76.70)	(57.80;77.60)	(59.40;75.60)	(57.80;76.70)
Min;max	30.6;103.0	41.8;103.0	36.9;100.4	30.6;100.7
CDLQI Score				
N	278	95	94	89
Mean (SD)	13.22 (6.53)	12.93 (6.27)	13.40 (7.26)	13.34 (6.04)
Median	13.00	13.00	13.00	13.00
Q1;Q3	(8.00;18.00)	(8.00;18.00)	(6.00;19.00)	(9.00;17.00)
Min;max	0.0;29.0	2.0;27.0	0.0;29.0	1.0;29.0
Adolescent Pruritus NRS (eDiary)				
N	284	96	96	92
Mean (SD)	7.61 (1.59)	7.49 (1.58)	7.83 (1.53)	7.49 (1.65)
Median	7.71	7.54	8.14	7.62
Q1;Q3	(6.57;8.82)	(6.62;8.71)	(6.71;8.93)	(6.43;8.71)
Min;max	1.4;10.0	1.4;10.0	4.1;10.0	2.1;10.0

1: Number of subjects in analysis set. N: Number of subjects with observation. SD: Standard deviation. Q1: 1st quartile. Q3: 3rd quartile. %: Percentage of subjects. Q2W: Every 2 weeks. IGA: Investigator's Global Assessment. EASI: Eczema Area and Severity Index. SCORAD: Scoring Atopic Dermatitis. CDLQI: Children's Dermatology Life Quality Index. NRS: Numeric rating scale.

Previous AD treatments, medical history, and concomitant medication

Panel 19 ***Previous AD treatments: full analysis set***

	Total (n=289)		Tralokinumab 150 mg Q2W (n=98)		Tralokinumab 300 mg Q2W (n=97)		Placebo (n=94)	
Previous AD treatment	N	(%)	N	(%)	N	(%)	N	(%)
Any previous treatment*	289	(100.0)	98	(100.0)	97	(100.0)	94	(100.0)
Antibiotics								
Yes	147	(50.9)	48	(49.0)	53	(54.6)	46	(48.9)
No	124	(42.9)	42	(42.9)	41	(42.3)	41	(43.6)
Topical corticosteroids								
Yes	289	(100.0)	98	(100.0)	97	(100.0)	94	(100.0)
Systemic steroids								
Yes	130	(45.0)	48	(49.0)	33	(34.0)	49	(52.1)
No	154	(53.3)	48	(49.0)	63	(64.9)	43	(45.7)
Calcineurin inhibitors								
Yes	169	(58.5)	53	(54.1)	60	(61.9)	56	(59.6)
No	105	(36.3)	38	(38.8)	34	(35.1)	33	(35.1)
Systemic immunosuppressant**								
Yes	61	(21.1)	22	(22.4)	19	(19.6)	20	(21.3)
No	227	(78.5)	76	(77.6)	78	(80.4)	73	(77.7)
Unknown	1	(0.3)					1	(1.1)
Mycophenolate								
Yes	8	(2.8)	4	(4.1)	1	(1.0)	3	(3.2)
No	273	(94.5)	92	(93.9)	95	(97.9)	86	(91.5)
Cyclosporine								
Yes	42	(14.5)	15	(15.3)	15	(15.5)	12	(12.8)
No	238	(82.4)	79	(80.6)	80	(82.5)	79	(84.0)
Methotrexate								
Yes	26	(9.0)	10	(10.2)	6	(6.2)	10	(10.6)
No	259	(89.6)	87	(88.8)	90	(92.8)	82	(87.2)
Azathioprine								
No	277	(95.8)	93	(94.9)	96	(99.0)	88	(93.6)
Monoclonal antibody/Dupilumab								
Yes	7	(2.4)	2	(2.0)	2	(2.1)	3	(3.2)
No	281	(97.2)	96	(98.0)	94	(96.9)	91	(96.8)

AD: Atopic Dermatitis. n: Number of subjects in analysis set. N: Number of subjects with observation. %: Percentage of subjects. Q2W: Every 2 weeks.
*) Any previous treatment confirmed as 'Yes'.
**) Includes methotrexate, cyclosporin, azathioprine, and mycophenolate.

Maintenance treatment period (Week 16 to Week 52)

Demographics

Overall, demographics were well balanced between treatment groups in the maintenance treatment period, however, some variation was observed due to the low number of subjects in each treatment group.

There were no clinically relevant differences in height, weight, BMI, or vital signs (blood pressure, pulse, and temperature) at baseline between treatment groups amongst subjects in the FAS assigned to maintenance treatment.

Panel 20 ***Demographics: subjects in FAS assigned to maintenance treatment***

	Week 16 Tralokinumab 150 mg Q2W responders		Week 16 Tralokinumab 300 mg Q2W responders		Week 16 Placebo responders
	Tralokinumab 150 mg Q2W (n=12)	Tralokinumab 150 mg Q4W (n=14)	Tralokinumab 300 mg Q2W (n=11)	Tralokinumab 300 mg Q4W (n=13)	Placebo (n=6)
Age (years)					
N	12	14	11	13	6
Mean (SD)	14.4 (1.8)	14.8 (1.8)	14.9 (2.0)	14.7 (1.8)	15.3 (1.4)
Median	13.5	15.5	16.0	14.0	15.5
Q1;Q3	(13.0;16.0)	(13.0;16.0)	(13.0;17.0)	(14.0;16.0)	(15.0;16.0)
Min;max	12;17	12;17	12;17	12;17	13;17
Sex, N (%)					
N (%)	12 (100.0)	14 (100.0)	11 (100.0)	13 (100.0)	6 (100.0)
Male	6 (50.0)	8 (57.1)	6 (54.5)	4 (30.8)	1 (16.7)
Female	6 (50.0)	6 (42.9)	5 (45.5)	9 (69.2)	5 (83.3)
Race, N (%)					
N (%)	12 (100.0)	14 (100.0)	11 (100.0)	13 (100.0)	6 (100.0)
White	6 (50.0)	8 (57.1)	7 (63.6)	7 (53.8)	3 (50.0)
Black or African American		1 (7.1)	1 (9.1)	3 (23.1)	2 (33.3)
Asian	3 (25.0)	5 (35.7)	1 (9.1)	3 (23.1)	1 (16.7)
Other	3 (25.0)		2 (18.2)		
Region, N (%)					
N (%)	12 (100.0)	14 (100.0)	11 (100.0)	13 (100.0)	6 (100.0)
North America	6 (50.0)	6 (42.9)	7 (63.6)	6 (46.2)	4 (66.7)
Europe	3 (25.0)	6 (42.9)	4 (36.4)	7 (53.8)	2 (33.3)
Asia	3 (25.0)	2 (14.3)			

Assigned to maintenance treatment period analysis set includes subjects who achieved clinical response at week 16.
n: Number of subjects in analysis set. N: Number of subjects with observation. SD: Standard deviation. Q1: 1st quartile. Q3: 3rd quartile. %: Percentage of subjects. Q2W: Every 2 weeks. Q4W: Every 4 weeks. FAS: Full analysis set.

Baseline disease severity

Overall, baseline disease severity was well balanced between treatment groups in the maintenance treatment period, however, some variation was observed due to the low number of subjects in each treatment group.

Panel 21 ***Baseline BSA, age of onset of AD and duration of AD: subjects in FAS assigned to maintenance treatment***

	Week 16 Tralokinumab 150 mg Q2W responders		Week 16 Tralokinumab 300 mg Q2W responders		Week 16 Placebo responders
	Tralokinumab 150 mg Q2W (n=12)	Tralokinumab 150 mg Q4W (n=14)	Tralokinumab 300 mg Q2W (n=11)	Tralokinumab 300 mg Q4W (n=13)	Placebo (n=6)
Baseline BSA (%)					
N	12	14	11	13	6
Mean (SD)	45.5 (21.8)	43.8 (18.4)	36.0 (16.8)	43.1 (22.8)	44.8 (16.9)
Median	47.0	41.5	31.0	37.0	45.5
Q1;Q3	(27.5;64.0)	(37.0;53.0)	(24.0;45.0)	(32.0;42.0)	(32.0;56.0)
Min;max	14;77	13;89	18;73	16;100	22;68
Age at onset of AD (years)					
N	12	14	11	13	6
Mean (SD)	2.7 (3.5)	2.9 (3.0)	3.5 (4.3)	2.2 (3.2)	3.2 (4.5)
Median	1.0	1.5	1.0	1.0	0.5
Q1;Q3	(0.0;3.5)	(1.0;5.0)	(1.0;7.0)	(0.0;2.0)	(0.0;9.0)
Min;max	0;10	0;8	0;12	0;10	0;9
Duration of AD (years)					
N	12	14	11	13	6
Mean (SD)	11.8 (4.2)	11.9 (4.3)	11.4 (4.3)	12.5 (3.4)	12.2 (4.7)
Median	12.5	13.0	12.0	14.0	13.5
Q1;Q3	(10.5;14.5)	(11.0;15.0)	(6.0;15.0)	(11.0;15.0)	(7.0;16.0)
Min;max	3;17	4;17	5;16	5;16	6;17

Assigned to maintenance treatment period analysis set includes subjects who achieved clinical response at week 16.
n: Number of subjects in analysis set. N: Number of subjects with observation. SD: Standard deviation. Q1: 1st quartile. Q3: 3rd quartile. Q2W: Every 2 weeks. Q4W: Every 4 weeks. BSA: Body surface area. AD: Atopic Dermatitis. FAS: Full analysis set.

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Panel 22 ***IGA, EASI, SCORAD, CDLQI, and Adolescent Worst Pruritus NRS (weekly average) at baseline: subjects in FAS***

	Week 16 Tralokinumab 150 mg Q2W responders		Week 16 Tralokinumab 300 mg Q2W responders		Week 16 Placebo responders
	Tralokinumab 150 mg Q2W (n=12)	Tralokinumab 150 mg Q4W (n=14)	Tralokinumab 300 mg Q2W (n=11)	Tralokinumab 300 mg Q4W (n=13)	Placebo (n=6)
Investigator's Global Assessment, N (%)					
N (%)	12 (100.0)	14 (100.0)	11 (100.0)	13 (100.0)	6 (100.0)
Moderate Disease	9 (75.0)	11 (78.6)	7 (63.6)	8 (61.5)	5 (83.3)
Severe Disease	3 (25.0)	3 (21.4)	4 (36.4)	5 (38.5)	1 (16.7)
EASI Score					
N	12	14	11	13	6
Mean (SD)	25.76 (11.78)	26.99 (7.14)	24.62 (7.23)	29.96 (14.34)	24.35 (9.96)
Median	21.90	25.73	23.20	27.10	21.75
Q1;Q3	(17.55;29.75)	(22.40;33.60)	(19.20;30.40)	(22.40;30.50)	(18.20;23.60)
Min;max	16.0;56.5	16.8;37.5	16.4;40.2	16.3;71.4	16.8;44.0
SCORAD Score					
N	12	14	11	13	6
Mean (SD)	63.06 (15.93)	64.43 (10.84)	64.19 (11.53)	67.46 (11.50)	55.88 (15.49)
Median	59.20	65.00	62.10	67.10	56.25
Q1;Q3	(52.35;70.60)	(59.70;68.10)	(59.40;70.60)	(63.60;74.70)	(48.20;58.10)
Min;max	41.8;94.7	42.9;83.6	44.7;87.8	37.7;85.7	34.6;81.9
CDLQI Score					
N	11	13	10	13	6
Mean (SD)	10.45 (6.89)	10.69 (5.60)	14.70 (9.14)	11.54 (8.06)	9.17 (6.08)
Median	9.00	10.00	17.50	6.00	8.50
Q1;Q3	(6.00;14.00)	(6.00;14.00)	(5.00;20.00)	(6.00;18.00)	(5.00;15.00)
Min;max	2.0;27.0	2.0;20.0	0.0;29.0	3.0;25.0	1.0;17.0

	Week 16 Tralokinumab 150 mg Q2W responders		Week 16 Tralokinumab 300 mg Q2W responders		Week 16 Placebo responders
	Tralokinumab 150 mg Q2W (n=12)	Tralokinumab 150 mg Q4W (n=14)	Tralokinumab 300 mg Q2W (n=11)	Tralokinumab 300 mg Q4W (n=13)	Placebo (n=6)
Adolescent Pruritus NRS (eDiary)					
N	12	13	11	13	6
Mean (SD)	7.55 (1.34)	7.17 (1.38)	7.66 (1.47)	8.02 (1.70)	6.28 (1.67)
Median	7.52	7.14	7.83	8.57	6.14
Q1;Q3	(6.83;8.32)	(6.14;8.57)	(6.00;8.71)	(7.00;8.80)	(4.86;6.57)
Min;max	5.0;10.0	4.4;9.0	5.3;10.0	4.1;10.0	4.7;9.3

Assigned to maintenance treatment period analysis set includes subjects who achieved clinical response at week 16.
n: Number of subjects in analysis set. N: Number of subjects with observation. SD: Standard deviation. Q1: 1st quartile. Q3: 3rd quartile. %: Percentage of subjects. Q2W: Every 2 weeks. Q4W: Every 4 weeks. IGA: Investigator's Global Assessment. EASI: Eczema Area and Severity Index. SCORAD: Scoring Atopic Dermatitis. CDLQI: Children's Dermatology Life Quality Index. NRS: Numeric rating scale. FAS: Full analysis set.

Panel 23 ***IGA, EASI, SCORAD, CDLQI, and Adolescent Worst Pruritus NRS (weekly average) at Week 16: subjects in FAS assigned to maintenance Treatment***

	Week 16 Tralokinumab 150mg Q2W responders		Week 16 Tralokinumab 300mg Q2W responders		Week 16 Placebo responders
	Tralokinumab 150 mg Q2W (n=12)	Tralokinumab 150 mg Q4W (n=14)	Tralokinumab 300 mg Q2W (n=11)	Tralokinumab 300 mg Q4W (n=13)	Placebo (n=6)
Investigator's Global Assessment, N (%)					
N	12	14	11	13	6
0-Clear	1 (8.3)	2 (14.3)	3 (27.3)	2 (15.4)	1 (16.7)
1-Almost clear	8 (66.7)	8 (57.1)	5 (45.5)	6 (46.2)	3 (50.0)
2-Mild disease	3 (25.0)	3 (21.4)	3 (27.3)	5 (38.5)	1 (16.7)
3-Moderate disease	0 (0.0)	1 (7.1)	0 (0.0)	0 (0.0)	1 (16.7)
4-Severe disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
EASI Score					
N	12	14	11	13	6
Mean (SD)	2.87 (3.39)	1.86 (1.68)	2.73 (3.48)	2.59 (2.44)	2.70 (2.11)
Median	1.15	1.85	0.80	2.30	2.40
Q1;Q3	(0.40;5.00)	(0.40;2.40)	(0.00;4.20)	(1.00;3.00)	(1.40;4.20)
Min;max	0.0;11.1	0.0;5.2	0.0;10.0	0.0;8.7	0.0;5.8
SCORAD Score					
N	12	14	11	13	6
Mean (SD)	19.43 (13.76)	17.25 (12.26)	17.61 (10.68)	18.69 (10.55)	22.08 (8.22)
Median	13.75	15.55	19.00	18.10	20.95
Q1;Q3	(10.40;29.05)	(8.80;25.60)	(7.90;24.30)	(12.50;24.10)	(17.10;27.60)
Min;max	0.6;47.2	0.0;40.4	1.6;37.2	0.0;41.9	11.2;34.7
CDLQI Score					
N	11	14	10	13	6
Mean (SD)	3.0 (3.7)	3.2 (3.0)	4.7 (3.0)	3.4 (3.7)	3.8 (2.4)
Median	2.0	3.5	5.0	2.0	4.5
Q1;Q3	(0.0;5.0)	(1.0;4.0)	(2.0;7.0)	(1.0;5.0)	(2.0;6.0)
Min;max	0;12	0;11	0;9	0;13	0;6
Adolescent Pruritus NRS					
N	11	12	10	12	5
Mean (SD)	3.763 (2.465)	2.552 (1.423)	4.315 (2.198)	2.470 (2.065)	3.966 (1.779)
Median	3.570	2.500	3.165	2.370	3.000
Q1;Q3	(1.800;4.290)	(1.570;3.785)	(2.710;6.430)	(0.570;3.750)	(2.800;5.000)
Min;max	1.25;10.00	0.00;4.71	2.14;8.43	0.00;6.40	2.43;6.60

n: Number of subjects in analysis set. N: Number of subjects with observation. SD: Standard deviation. Q1: 1st quartile. Q3: 3rd quartile. %: Percentage of subjects. Q2W: Every 2 weeks. Q4W: Every 4 weeks. IGA: Investigator's Global Assessment. EASI: Eczema Area and Severity Index. SCORAD: Scoring Atopic Dermatitis. CDLQI: Children's Dermatology Life Quality Index. NRS: Numeric rating scale.

Concomitant medication

Initial treatment period (Week 0 to Week 16)

The most frequently reported concomitant medications were within the 'dermatologicals' category, with nearly all subjects (96.9% to 100.0% across treatment groups) reporting concomitant use of dermatological medication. The most common medications in this category were 'emollients and protectives', which were were reported by nearly all subjects in line with the protocol requirement for use of emollients as background treatment, and 'corticosteroids, dermatological preparations', which were primarily given as rescue medication for AD.

Use of concomitant medication within ATC level 1 categories was generally well balanced between treatment groups, with the exception of 'antiinfectives for systemic use' which were used less frequently in the tralokinumab 300 mg Q2W group (16.5% of the subjects) compared with tralokinumab 150 mg Q2W (28.6% of the subjects) and placebo (28.7% of the subjects).

Maintenance treatment period (Week 16 to Week 52)

The overall pattern in the use of concomitant medication was similar to that observed in the initial treatment period, however data should be interpreted with caution due to the low number of subjects in each treatment group.

Open-label treatment period (Week 16 to Week 52)

During the open-label treatment period, 99.5% of the subjects used any concomitant medications. The pattern in the use of concomitant medication was similar to that observed in the tralokinumab groups in the initial treatment period, except for the use of TCS and 'antiinfectives for systemic use'. The use of TCS was higher in the open-label treatment group (50.0%) compared with the tralokinumab 300 mg Q2W group (29.9%) and the tralokinumab 150 mg Q2W group (33.7%), which reflected that mild to moderate potency TCS were allowed in the open-label treatment period while it was considered rescue medication in the initial treatment period. The use of 'antiinfectives for systemic use' was higher in the open-label treatment group (34.1%) compared with the tralokinumab 300 mg Q2W group (16.5%) and the tralokinumab 150 mg Q2W group (28.6%), which may reflect the longer duration of the open-label treatment period (i.e. that subjects were more likely to experience an infection when observed for longer time).

Rescue medication

Use of rescue medication from baseline to Week 16 was included as another endpoint to evaluate the efficacy of tralokinumab compared with placebo on healthcare resource utilisation.

Initial treatment period (Week 0 to Week 16)

The use of rescue medication in the initial treatment period was slightly higher with tralokinumab 150 mg Q2W compared with tralokinumab 300 mg Q2W, but lower in both tralokinumab groups compared with the placebo group. The vast majority of the rescue medication was TCS which was in line with the protocol instruction to limit first step of rescue medication to topical treatments. The use of moderate TCS (group II) and potent TCS (group III) was higher in the placebo group compared with the tralokinumab groups, indicating that more potent TCS were required to alleviate intolerable AD symptoms in the placebo group. In all 3 treatment groups, the majority of subjects who used rescue medication remained on IMP treatment until Week 16.

Panel 24 ***Rescue medication by type, initial treatment period: full analysis set***

	Tralokinumab 150 mg Q2W (n=98)		Tralokinumab 300 mg Q2W (n=97)		Placebo (n=94)	
	N	(%)	N	(%)	N	(%)
Any rescue medication	33	(33.7)	29	(29.9)	53	(56.4)
Topical						
Corticosteroids	33	(33.7)	29	(29.9)	51	(54.3)
Other*	3	(3.1)	5	(5.2)	8	(8.5)
Systemic						
Corticosteroids	1	(1.0)	1	(1.0)	5	(5.3)
Immunosuppressants**			1	(1.0)	1	(1.1)

Q2W: Every 2 weeks. n: Number of subjects in analysis set. N: Number of subjects with observation. %: Percentage of subjects.
*) Includes e.g. pimecrolimus, tacrolimus, crisaborole.
**) Includes methotrexate, cyclosporin, azathioprine, and mycophenolate.
***) Includes other immunosuppressants, e.g. dupilumab.

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Use of rescue medication by baseline IGA

The use of rescue medication was higher in subjects with severe disease at baseline compared with subjects with moderate disease at baseline. Regardless of the disease severity at baseline, the use of rescue medication was higher in the placebo group compared with the tralokinumab groups. The vast majority of rescue medication was TCS both in subjects with moderate and severe disease in all 3 treatment groups.

Panel 25 ***Use of rescue medication by baseline IGA, initial treatment period: full analysis set***

Baseline disease severity	Tralokinumab 150 mg Q2W (n=98)	Tralokinumab 300 mg Q2W (n=97)	Placebo (n=94)
Moderate disease (IGA=3)			
Subjects in FAS	54	49	51
Subjects with any rescue medication (%)	14 (25.9)	10 (20.4)	27 (52.9)
Severe disease (IGA=4)			
Subjects in FAS	44	48	43
Subjects with any rescue medication (%)	19 (43.2)	19 (39.6)	26 (60.5)

Abbreviations: FAS = full analysis set; IGA = Investigator's Global Assessment; n = number of subjects in analysis set; Q2W = every 2 weeks.

Use of rescue medication by region

The use of rescue medication was comparable between North American and European subjects but higher use of rescue medication was observed for Australian and Asian subjects. The use of rescue medication was higher in the placebo group compared with the tralokinumab groups in all regions. The observation of higher use of rescue medication in Australian and Asian subjects may be a chance observation resulting from the low number of subjects in these subgroups. Furthermore, the observation in Australian subjects may also be driven by a higher proportion of subjects with severe disease at baseline in this subgroup.

Panel 26 ***Use of rescue medication by region, initial treatment period: full analysis set***

Region	Tralokinumab 150 mg Q2W (n=98)	Tralokinumab 300 mg Q2W (n=97)	Placebo (n=94)
North America			
Subjects in FAS	50	48	47
Subjects with any rescue medication (%)	14 (28.0)	12 (25.0)	21 (44.7)
Europe			
Subjects in FAS	33	33	32
Subjects with any rescue medication (%)	13 (39.4)	5 (15.2)	17 (53.1)
Australia			
Subjects in FAS	5	5	4
Subjects with any rescue medication (%)	2 (40.0)	4 (80.0)	4 (100.0)
Asia			
Subjects in FAS	10	11	11
Subjects with any rescue medication (%)	4 (40.0)	8 (72.7)	11 (100.0)

Abbreviations: FAS = full analysis set; n = number of subjects in analysis set; Q2W = every 2 weeks

Maintenance treatment period (Week 16 to Week 52)

The use of rescue medication was comparable between all treatment groups in the maintenance treatment period, however data should be interpreted with caution due to the low number of subjects in each treatment group. The use of rescue medication in the maintenance treatment period was generally lower than in the initial treatment period, and only topical treatments (mainly TCS) were used as rescue medication.

Panel 27 ***Rescue medication by type, maintenance treatment period: subjects in FAS assigned to maintenance treatment period***

	Week 16 Tralokinumab 150 mg Q2W responders				Week 16 Tralokinumab 300 mg Q2W responders				Week 16 Placebo responders	
	Tralokinumab 150 mg Q2W (n=12)		Tralokinumab 150 mg Q4W (n=14)		Tralokinumab 300 mg Q2W (n=11)		Tralokinumab 300 mg Q4W (n=13)		Placebo (n=6)	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Any rescue medication	3	(25.0)	3	(21.4)	2	(18.2)	1	(7.7)	1	(16.7)
Topical										
Corticosteroids	3	(25.0)	3	(21.4)	2	(18.2)	1	(7.7)		
Other*							1	(7.7)	1	(16.7)

Assigned to maintenance treatment period analysis set includes subjects who achieved clinical response at week 16.
Q2W: Every 2 weeks. Q4W: Every 4 weeks. n: Number of subjects in analysis set. N: Number of subjects with observation. %: Percentage of subjects. FAS: Full analysis set.
*) Includes e.g. pimecrolimus, tacrolimus, crisaborole.
**) Includes methotrexate, cyclosporin, azathioprine, and mycophenolate.
***) Includes other immunosuppressants, e.g. dupilumab.

Open-label treatment period (Week 16 to Week 52)

The definition of rescue medication in the open-label treatment period was different from the initial and maintenance treatment periods as use of mild to moderate TCS was allowed. Use of rescue medication was low in the open-label treatment period, which is consistent with the majority of the rescue medication used in the initial treatment period being TCS and the allowance of mild to moderate TCS in the open-label treatment period. The majority of the rescue medication used in the open-label treatment period were topical treatments (primarily higher potency TCS).

Panel 28 ***Rescue medication by type, open-label treatment period: subjects in FAS transferred to open-label treatment***

	Tralokinumab 300 mg Q2W + optional TCS (n=234)	
	N	(%)
Any rescue medication	18	(7.7)
Topical		
Corticosteroids	13	(5.6)
Other*	3	(1.3)
Systemic		
Corticosteroids	2	(0.9)
Other***	1	(0.4)

Q2W: Every 2 weeks. TCS: topical corticosteroid. n: Number of subjects in analysis set. N: Number of subjects with observation. %: Percentage of subjects. FAS: Full analysis set.
*) Includes e.g. crisaborole.
**) Includes methotrexate, cyclosporin, azathioprine, and mycophenolate.
***) Includes other immunosuppressants, e.g. dupilumab.

Numbers analysed

Full analysis set

All subjects randomised to initial treatment who were exposed to IMP and not randomised at investigational sites with GCP non-compliance issues were included in the full analysis set (FAS) and were analysed for efficacy up to Week 16 (Visit 11). 301 subjects were randomised to treatment, of which 3 subjects were not dosed and 9 subjects were randomised at investigational sites with GCP non-compliance issues. Hence, the FAS comprised 289 subjects.

Per protocol analysis set

2 subjects from the FAS were excluded from the per protocol analysis set because they provided no IGA or EASI assessments after the start of the treatment. Hence, the per protocol analysis set comprised 287 subjects.

Maintenance analysis set

The maintenance analysis set included all subjects who received tralokinumab in the initial treatment period, were not randomised at investigational sites with GCP non-compliance issues, and were re-randomised to maintenance treatment. Hence, the maintenance analysis set comprised 50 subjects.

Safety analysis set

All 289 subjects from the FAS were included in the safety analysis set.

Maintenance safety analysis set

The maintenance safety analysis set comprised all subjects who were assigned to maintenance treatment, were not randomised at investigational sites with GCP non-compliance issues, and received at least 1 dose of maintenance treatment. Hence, the maintenance safety analysis set comprised 56 subjects.

Open-label safety analysis set

The open-label safety analysis set comprised all subjects who transferred to open-label treatment during the trial, were not randomised at investigational sites with GCP non-compliance issues, and received at least 1 dose of open-label treatment. Hence, the open-label safety analysis set comprised 234 subjects.

Outcomes and estimation

The first step of the testing hierarchy was the test of IGA 0/1 at Week 16 between tralokinumab 300 mg Q2W and placebo, which was evaluated at a 5% significance level. The difference between tralokinumab 300 mg Q2W and placebo in IGA 0/1 at Week 16 was statistically significant with a p-value of 0.002.

As the first step in the testing hierarchy was statistically significant, the second step (i.e. EASI75 at Week 16) was tested and evaluated at a 5% significance level, and the difference between tralokinumab 300 mg Q2W and placebo was also statistically significant for EASI75 at Week 16 with a p-value of <0.001.

As the first and second steps in the testing hierarchy were statistically significant, the significance level (alpha) was divided between the analyses of the 3 secondary endpoints for tralokinumab 300 mg Q2W (i.e. reduction of Adolescent Worst Pruritus NRS [weekly average] ≥4 from baseline to Week 16, change in SCORAD from baseline to Week 16, and change in CDLQI from baseline to Week 16) and the analyses of the primary and secondary endpoints for tralokinumab 150 mg Q2W. The significance level was evenly split, i.e. the secondary endpoints for tralokinumab 300 mg Q2W and the primary and secondary endpoints for tralokinumab 150 mg Q2W were both tested at alpha = 2.5%. However, if all secondary endpoints were found to be statistically significant for one dose, alpha could be recycled for testing of the other dose.

The evaluations of the 3 secondary endpoints for tralokinumab 300 mg Q2W used the Holm- Bonferroni method for 3 ordered p-values at a 2.5% significance level to adjust for multiplicity. According to the Holm-Bonferroni method, the p-values were ordered by increasing value and evaluated against the 3 alpha levels of 0.025/3, 0.025/2, and 0.025/1. For both ≥4-point reduction in Adolescent Worst Pruritus NRS and change in SCORAD, the p-value was <0.001, hence these 2 tests were statistically significant as the p-values were below 0.025/3 and 0.025/2. For change in CDLQI, the p-value was 0.007, hence this test was statistically significant as the p-value was below 0.025/1.

Since all tests in the above steps were statistically significant, the hypotheses for tralokinumab 150 mg Q2W could be tested at a 5% significance level. The first step within the testing hierarchy for tralokinumab 150 mg Q2W was the test of IGA 0/1 at Week 16 between tralokinumab 150 mg Q2W and placebo. The difference between tralokinumab 150 mg Q2W and placebo in IGA 0/1 at Week 16 was statistically significant with a p-value <0.001.

As the first step in the testing hierarchy for tralokinumab 150 mg Q2W was statistically significant, the second step (i.e. EASI75 at Week 16) was tested and evaluated at a 5% significance level, and the difference between tralokinumab 150 mg Q2W and placebo was also statistically significant for EASI75 at Week 16 with a p-value of <0.001.

As the first and second steps in the testing hierarchy for tralokinumab 150 mg Q2W were statistically significant, the 3 secondary endpoints for tralokinumab 150 mg Q2W were evaluated using the Holm-Bonferroni method for 3 ordered p-values at a 5% significance level to adjust for multiplicity. The p-values were ordered by increasing value and evaluated against the 3 alpha levels of 0.05/3, 0.05/2, and 0.05/1. For both ≥4-point reduction in Adolescent Worst Pruritus NRS and change in SCORAD, the p-value was <0.001 hence these 2 tests were statistically significant as the p-values were below 0.05/3 and 0.05/2. For change in CDLQI, the p-value was 0.040, hence this test was statistically significant as the p-value was below 0.05/1.

Primary endpoints

There were 2 primary endpoints in this trial:

- IGA score of 0 (clear) or 1 (almost clear) at Week 16.
- EASI75 at Week 16.

All analyses of the primary endpoints were based on the full analysis set and analysed according to their randomised treatment groups.

The following 3 estimands were defined for the primary endpoints where the applied estimands incorporated 2 main types of intercurrent events (initiation of rescue medication and permanent discontinuation of IMP) that influenced how the treatment effect was estimated:

Primary estimand: 'composite':

- assessed the treatment difference in response rate of IGA 0/1 and EASI75 after 16 weeks achieved without rescue medication between Week 2 and Week 16, regardless of treatment discontinuation.

Secondary estimand: 'hypothetical':

- assessed the treatment difference in response rate of IGA 0/1 and EASI75 after 16 weeks if all subjects adhered to the treatment regimen in the sense that they did not discontinue IMP permanently and no rescue medication was used from Week 2 to Week 16.

Tertiary estimand: 'treatment policy':

- assessed the treatment difference in response rate of IGA 0/1 and EASI75 after 16 weeks regardless of rescue medication and treatment discontinuation.

IGA 0/1 at Week 16 in the full analysis set

*Panel 29 I**GA 0/1 responders at Week 16 (primary endpoint): full analysis set***

IGA 0/1 at Week 16	Tralokinumab 150 mg Q2W (n= 98)	Tralokinumab 300 mg Q2W (n= 97)	Placebo (n= 94)
Primary estimand: Composite &,#			
Primary analysis			
Responders (%)*	21/ 98(21.4)	17/ 97(17.5)	4/ 94(4.3)
Diff. in percentage (95% CI)**	17.5 (8.4,26.6)	13.8 (5.3,22.3)	
p value***	<0.001	0.002	
Sensitivity analysis 1 ##			
Responders (%)*	21/ 98(21.4)	17/ 97(17.5)	4/ 94(4.3)
Diff. in percentage (95% CI)**	17.5 (8.4,26.6)	13.8 (5.3,22.3)	
p value***	<0.001	0.002	
Sensitivity analysis 2 ###			
Responders (%)*	21/ 98(21.4)	17/ 97(17.5)	5/ 94(5.3)
Diff. in percentage (95% CI)**	16.4 (7.2,25.7)	12.8 (4.1,21.4)	
p value***	<0.001	0.005	
Secondary estimand: Hypothetical +			
Primary analysis ++			
Responders (%)*	31.0/ 98(31.6)	25.4/ 97(26.2)	18.4/ 94(19.6)
Diff. in percentage (95% CI)**	12.5 (-3.5,28.4)	7.2 (-9.0,23.4)	
p value***	0.13	0.38	
Sensitivity analysis +++			
Responders (%)*	30.5/ 98(31.1)	25.2/ 97(25.9)	18.6/ 94(19.8)
Diff. in percentage (95% CI)**	11.8 (-2.7,26.2)	6.6 (-7.7,21.0)	
p value***	0.11	0.36	
Tertiary estimand: Treatment policy			
Sensitivity analysis $$			
Responders (%)*	23/ 98(23.5)	20/ 97(20.6)	5/ 94(5.3)
Diff. in percentage (95% CI)**	18.5 (9.0,28.0)	15.5 (6.4,24.6)	
p value***	<0.001	0.001	

An analysis based on the per protocol analysis set was repeated for the primary analysis of the primary estimand. The result based on this analysis set supported the results based on the full analysis set. The estimated difference to placebo was 14.0% (p=0.002) with tralokinumab 300 mg Q2W and 17.4% (p<0.001) with tralokinumab 150 mg Q2W. The proportion of responders was 17.7% in the tralokinumab 300 mg Q2W group, 21.4% in the tralokinumab 150 mg Q2W group, and 4.3% in the placebo group.

EASI75 at Week 16 in the full analysis set

Panel 30 ***EASI75 responders at Week 16 (primary endpoint): full analysis set***

EASI75 at Week 16	Tralokinumab 150 mg Q2W (n= 98)	Tralokinumab 300 mg Q2W (n= 97)	Placebo (n= 94)
Primary estimand: Composite &,#			
Primary analysis			
Responders (%)*	28/ 98(28.6)	27/ 97(27.8)	6/ 94(6.4)
Diff. in percentage (95% CI)**	22.5 (12.4,32.6)	22.0 (12.0,32.0)	
p value***	<0.001	<0.001	
Sensitivity analysis 1 ##			
Responders (%)*	28/ 98(28.6)	27/ 97(27.8)	5/ 94(5.3)
Diff. in percentage (95% CI)**	23.5 (13.6,33.5)	23.0 (13.1,32.9)	
p value***	<0.001	<0.001	
Sensitivity analysis 2 ###			
Responders (%)*	28/ 98(28.6)	27/ 97(27.8)	7/ 94(7.4)
Diff. in percentage (95% CI)**	21.4 (11.2,31.6)	21.0 (10.8,31.1)	
p value***	<0.001	<0.001	
Secondary estimand: Hypothetical +			
Primary analysis ++			
Responders (%)*	37.9/ 98(38.7)	34.6/ 97(35.6)	13.8/ 94(14.7)
Diff. in percentage (95% CI)**	24.5 (9.8,39.1)	21.6 (7.6,35.6)	
p value***	0.001	0.002	
Sensitivity analysis +++			
Responders (%)*	35.0/ 98(35.7)	32.7/ 97(33.7)	14.0/ 94(14.9)
Diff. in percentage (95% CI)**	21.2 (7.5,34.9)	19.3 (5.7,33.0)	
p value***	0.002	0.006	
Tertiary estimand: Treatment policy			
Sensitivity analysis $$			
Responders (%)*	39/ 98(39.8)	36/ 97(37.1)	19/ 94(20.2)
Diff. in percentage (95% CI)**	20.5 (8.3,32.7)	17.3 (5.2,29.4)	
p value***	0.002	0.007	

An analysis based on the per protocol analysis set was repeated for the primary analysis of the primary estimand. The result based on this analysis set supported the results based on the full analysis set. The estimated difference to placebo was 22.2% (p<0.001) with tralokinumab 300 mg Q2W and 22.3% (p<0.001) with tralokinumab 150 mg Q2W. The proportion of responders was 28.1% in the tralokinumab 300 mg Q2W group, 28.6% in the tralokinumab 150 mg Q2W group, and 6.5% in the placebo group.

Confirmatory secondary endpoints

To evaluate the efficacy of tralokinumab 300 mg Q2W and tralokinumab 150 mg Q2W on itch, severity and extent of AD, and health-related quality of life, the trial included the following 3 secondary endpoints:

- Reduction of Adolescent Worst Pruritus NRS (weekly average) ≥4 from baseline to Week 16
- Change in SCORAD from baseline to Week 16
- Change in CDLQI score from baseline to Week 16

All analyses of the secondary endpoints were based on the full analysis set.

For each secondary endpoint, 3 estimands were defined where the applied estimands incorporated 2 main types of intercurrent events that influenced how the treatment effects were estimated, i.e. initiation of rescue medication and permanent discontinuation of IMP.

Reduction of Adolescent Worst Pruritus NRS (weekly average) ≥4 from baseline to Week 16

- Primary estimand: 'composite':
  - assessed the treatment difference in response rate of Adolescent Worst Pruritus NRS after 16 weeks achieved without rescue medication between Week 2 and Week 16, regardless of treatment discontinuation.
- Secondary estimand: 'hypothetical':
  - assessed the treatment difference in response rate of Adolescent Worst Pruritus NRS after 16 weeks if all subjects adhered to the treatment regimen in the sense that they did not discontinue IMP permanently and no rescue medication was used from Week 2 to Week 16.
- Tertiary estimand: 'treatment policy':
  - assessed the treatment difference in response rate of Adolescent Worst Pruritus NRS after 16 weeks regardless of rescue medication and treatment discontinuation.

The proportion of subjects with a reduction of Adolescent Worst Pruritus NRS (weekly average) ≥4 from baseline to Week 16, among subjects with Adolescent Worst Pruritus NRS (weekly average) of ≥4 at baseline, was statistically significantly higher in both tralokinumab groups compared with the placebo group:

- The estimated differences to placebo were 21.7% ($p<0.001$) with tralokinumab 300 mg Q2W and 19.9% ($p<0.001$) with tralokinumab 150 mg Q2W, with 25.0% responders in the tralokinumab 300 mg Q2W group, 23.2% responders in the tralokinumab 150 mg Q2W group, and 3.3% responders in the placebo group (primary analysis of the primary estimand).

Panel 31 ***Reduction of Adolescent Worst Pruritus NRS (weekly average) of ≥4 from baseline to Week 16, based on subjects with a baseline Adolescent Worst Pruritus NRS (weekly average) of ≥4: full analysis set***

Adolescent Pruritus NRS Reduction ≥ 4	Tralokinumab 150 mg Q2W (n= 95)	Tralokinumab 300 mg Q2W (n= 96)	Placebo (n= 90)
Primary estimand: Composite &,#			
Primary analysis			
Responders (%)*	22/ 95(23.2)	24/ 96(25.0)	3/ 90(3.3)
Diff. in percentage (95% CI)**	19.9 (10.6,29.2)	21.7 (12.3,31.1)	
p value***	<0.001	<0.001	
Sensitivity analysis 1 ##			
Responders (%)*	22/ 95(23.2)	24/ 96(25.0)	3/ 90(3.3)
Diff. in percentage (95% CI)**	19.9 (10.6,29.2)	21.7 (12.3,31.1)	
p value***	<0.001	<0.001	
Sensitivity analysis 2 ###			
Responders (%)*	25/ 95(26.3)	28/ 96(29.2)	3/ 90(3.3)
Diff. in percentage (95% CI)**	23.0 (13.4,32.7)	25.9 (16.1,35.7)	
p value***	<0.001	<0.001	
Secondary estimand: Hypothetical +			
Primary analysis ++			
Responders (%)*	32.3/ 95(34.0)	37.1/ 96(38.6)	14.1/ 90(15.7)
Diff. in percentage (95% CI)**	18.6 (3.7,33.5)	23.1 (8.0,38.2)	
p value***	0.015	0.003	
Sensitivity analysis++			
Responders (%)*	31.1/ 95(32.7)	33.7/ 96(35.1)	14.0/ 90(15.6)
Diff. in percentage (95% CI)**	17.4 (3.2,31.7)	19.7 (5.8,33.5)	
p value***	0.016	0.005	
Tertiary estimand: Treatment policy			
Sensitivity analysis $$			
Responders (%)*	30/ 95(31.6)	32/ 96(33.3)	16/ 90(17.8)
Diff. in percentage (95% CI)**	14.3 (2.0,26.7)	15.7 (3.4,27.9)	
p value***	0.025	0.014	

Change in SCORAD and CDLQI from baseline to Week 16

- Primary estimand ('hypothetical'):
  - assessed the treatment difference in change from baseline to Week 16 in SCORAD and CDLQI if all subjects adhered to the treatment regimen in the sense that they did not discontinue IMP permanently and no rescue medication was used from Week 2 to Week 16.

Secondary estimand ('treatment policy'):

- assessed the treatment difference in change from baseline to Week 16 in SCORAD and CDLQI, regardless of rescue medication use and treatment discontinuation.

• Tertiary estimand ('composite'):

- assessed the treatment difference in change from baseline to Week 16 in SCORAD and CDLQI achieved without rescue medication between Week 2 and Week 16, regardless of treatment discontinuation

The changes in SCORAD and CDLQI from baseline to Week 16 were statistically significantly larger in the tralokinumab groups compared with the placebo group:

- For SCORAD, the estimated differences to placebo were -19.7 points (p<0.001) with tralokinumab 300 mg Q2W and -18.0 points (p<0.001) with tralokinumab 150 mg Q2W, with an adjusted mean change from baseline of -29.1 points in the tralokinumab 300 mg Q2W group, -27.5 points in the tralokinumab 150 mg Q2W group, and -9.5 points in the placebo group (primary analysis of the primary estimand).
- For CDLQI, the estimated differences to placebo were -2.6 points (p=0.007) with tralokinumab 300 mg Q2W and -2.0 points (p=0.040) with tralokinumab 150 mg Q2W, with an adjusted mean change from baseline of -6.7 points in the tralokinumab 300 mg Q2W group, -6.1 points in the tralokinumab 150 mg Q2W group, and -4.1 points in the placebo group (primary analysis of the primary estimand).

Panel 32 ***Change from baseline in SCORAD at Week 16: full analysis set***

Change from baseline to Week 16 in SCORAD	Tralokinumab 150 mg Q2W (n= 98)	Tralokinumab 300 mg Q2W (n= 97)	Placebo (n= 94)
Primary estimand: Hypothetical *			
Primary analysis +			
Adjusted mean change (SE)	-27.5 (2.4)	-29.1 (2.4)	-9.5 (3.0)
95% CI	-32.3 to -22.7	-33.8 to -24.4	-15.3 to -3.6
Difference (95% CI)	-18.0 (-25.6, -10.4)	-19.7 (-27.1, -12.2)	
p value	<0.001	<0.001	
Sensitivity analysis ++			
Adjusted mean change (SE)	-23.5 (2.7)	-26.0 (2.5)	-9.7 (3.3)
95% CI	-28.8 to -18.1	-30.9 to -21.0	-16.1 to -3.2
Difference (95% CI)	-13.8 (-21.2,-6.4)	-16.3 (-23.9,-8.7)	
p value	<0.001	<0.001	
Secondary estimand: Treatment policy			
Sensitivity analysis $			
Adjusted mean change (SE)	-28.0 (2.3)	-29.8 (2.1)	-16.6 (2.4)
95% CI	-32.4 to -23.6	-34.0 to -25.6	-21.3 to -11.9
Difference (95% CI)	-11.4 (-17.5,-5.2)	-13.2 (-19.5,-7.0)	
p value	<0.001	<0.001	
Tertiary estimand: Composite			
Primary analysis #			
Adjusted mean change (SE)	-18.9 (2.2)	-21.7 (2.2)	-2.7 (2.2)
95% CI	-23.3 to -14.6	-26.0 to -17.5	-7.1 to 1.7
Difference (95% CI)	-16.3 (-22.4,-10.1)	-19.1 (-25.2,-12.9)	
p value	<0.001	<0.001	

Change from baseline in CDLQI score at Week 16

Panel 33 ***Change from baseline in CDLQI at Week 16: full analysis set***

Change from baseline to Week 16 in CDLQI	Tralokinumab 150 mg Q2W (n= 95)	Tralokinumab 300 mg Q2W (n= 94)	Placebo (n= 89)
Primary estimand: Hypothetical *			
Primary analysis +			
Adjusted mean change (SE)	-6.1 (0.6)	-6.7 (0.6)	-4.1 (0.7)
95% CI	-7.3 to -4.9	-7.9 to -5.5	-5.6 to -2.7
Difference (95% CI)	-2.0 (-3.9, -0.1)	-2.6 (-4.5, -0.7)	
p value	0.040	0.007	
Sensitivity analysis ++			
Adjusted mean change (SE)	-5.5 (0.7)	-6.2 (0.7)	-3.8 (0.9)
95% CI	-6.9 to -4.1	-7.5 to -4.9	-5.5 to -2.1
Difference (95% CI)	-1.7 (-3.5,0.2)	-2.4 (-4.4,-0.4)	
p value	0.078	0.017	
Secondary estimand: Treatment policy			
Sensitivity analysis $			
Adjusted mean change (SE)	-6.3 (0.6)	-7.1 (0.6)	-4.8 (0.6)
95% CI	-7.5 to -5.1	-8.2 to -6.0	-6.0 to -3.6
Difference (95% CI)	-1.6 (-3.2,0.0)	-2.3 (-3.9,-0.7)	
p value	0.055	0.005	
Tertiary estimand: Composite			
Primary analysis #			
Adjusted mean change (SE)	-3.9 (0.6)	-5.0 (0.6)	-0.8 (0.6)
95% CI	-5.0 to -2.7	-6.1 to -3.8	-2.0 to 0.4
Difference (95% CI)	-3.1 (-4.8,-1.4)	-4.2 (-5.9,-2.5)	
p value	<0.001	<0.001	

ANCOVA: Analysis of covariance, CDLQI: Children's Dermatology Life Quality Index, CI:

Additional secondary endpoints

The efficacy of tralokinumab was also demonstrated by the efficacy assessments conducted through the initial treatment period to support the primary and confirmatory secondary endpoints and by the other endpoints related to the efficacy of tralokinumab over time on severity and extent of AD, itch, and HRQoL.

IGA

The proportion of IGA 0/1 responders was higher in the tralokinumab groups compared with the placebo group from Week 4 to Week 16, with a separation between the treatment groups (i.e. $p<0.05$ for comparisons) from Week 10 to Week 16 for tralokinumab 300 mg Q2W and from Week 6 to Week 16 for tralokinumab 150 mg Q2W.

EASI

The proportion of EASI75 responders was higher in both the tralokinumab 300 mg Q2W and tralokinumab 150 mg Q2W groups compared with the placebo group at each scheduled assessment from Week 4 to Week 16, with a separation between both tralokinumab groups and the placebo group (i.e. $p<0.05$ for comparisons) from Week 4 to Week 16.

The proportions of EASI50 and EASI90 responders at Week 16 were higher in both the tralokinumab 300 mg Q2W and tralokinumab 150 mg Q2W groups compared with the placebo group:

- For EASI50, the estimated differences to placebo were 38.5% ($p<0.001$) with tralokinumab 300 mg Q2W and 32.4% ($p<0.001$) for tralokinumab 150 mg Q2W, with 51.5% responders in the

tralokinumab 300 mg Q2W group, 45.9% responders in the tralokinumab 150 mg Q2W group, and 13.8% responders in the placebo group.

- For EASI90, the estimated differences to placebo were 13.7% (p=0.002) with tralokinumab 300 mg Q2W and 15.3% (p<0.001) for tralokinumab 150 mg Q2W, with 17.5% responders in the tralokinumab 300 mg Q2W group, 19.4% responders in the tralokinumab 150 mg Q2W group, and 4.3% responders in the placebo group.

Adolescent Worst Pruritus NRS

The absolute and percent change from baseline in Adolescent Worst Pruritus NRS were larger in both tralokinumab groups compared with the placebo group at each scheduled assessment through the initial treatment period. For tralokinumab 300 mg Q2W, separation to placebo (i.e. p<0.05 for comparisons) was observed from Week 7 to Week 16 for the absolute change from baseline in Adolescent Worst Pruritus NRS and from Week 9 to Week 16 for the percent change from baseline in Adolescent Worst Pruritus NRS. For tralokinumab 150 mg Q2W, separation to placebo was observed from Week 6 to Week 16 for the absolute change from baseline in Adolescent Worst Pruritus NRS.

The differences between the tralokinumab groups and the placebo group in the proportion of subjects with a ≥3-point reduction in Adolescent Worst Pruritus NRS from baseline to Week 16 were 20.3% (p<0.001) with tralokinumab 300 mg Q2W and 21.8% (p<0.001) with tralokinumab 150 mg Q2W. The proportion of responders was 29.2% in the tralokinumab 300 mg Q2W group, 30.5% in the tralokinumab 150 mg Q2W group, and 8.8% in the placebo group.

The proportion of subjects with a ≥4-point reduction in Adolescent Worst Pruritus NRS from baseline was higher in the tralokinumab 300 mg Q2W and tralokinumab 150 mg Q2W groups than in the placebo group at each scheduled assessment in the initial treatment period. Separation between tralokinumab 300 mg Q2W and placebo (i.e. p<0.05 for comparisons) was observed from Week 9 to Week 16 while separation between tralokinumab 150 mg Q2W and placebo was observed from Week 6 to Week 16.

The proportion of subjects with a ≥3-point reduction in Adolescent Worst Pruritus NRS from baseline was higher in the tralokinumab 300 mg Q2W and tralokinumab 150 mg Q2W groups than in the placebo group at each scheduled assessment in the initial treatment period. Both separation between tralokinumab 300 mg Q2W and placebo and between tralokinumab 150 mg Q2W and placebo (i.e. p<0.05 for comparisons) were observed from Week 6 to Week 16.

SCORAD

The absolute and percent change from baseline in SCORAD were larger in both tralokinumab groups compared with the placebo group at each scheduled assessment through the initial treatment period. For tralokinumab 300 mg Q2W, separation to placebo (i.e. p<0.05 for comparisons) was observed from Week 2 to Week 16 for both the absolute change and the percent change from baseline in SCORAD. For tralokinumab 150 mg Q2W, separation to placebo was observed from Week 4 to Week 16 for both the absolute change and the percent change from baseline in SCORAD.

The proportion of subjects with SCORAD75 was higher in the tralokinumab 300 mg Q2W and tralokinumab 150 mg Q2W groups compared with the placebo group at each scheduled assessment from Week 4 to Week 16. Separation between tralokinumab 300 mg Q2W and placebo (i.e. p<0.05 for comparisons) was observed from Week 10 to Week 16 while separation between tralokinumab 150 mg Q2W and placebo was observed from Week 8 to Week 16. At Week 16, the estimated difference to placebo was 11.5% (p=0.002) with tralokinumab 300 mg Q2W and 15.6% (p<0.001) with tralokinumab 150 mg Q2W.

The proportion of subjects with SCORAD50 was higher in the tralokinumab 300 mg Q2W and tralokinumab 150 mg Q2W groups compared with the placebo group at each scheduled assessment from Week 4 to Week 16. Both separation between tralokinumab 300 mg Q2W and placebo and between tralokinumab 150 mg

Q2W and placebo (i.e. p<0.05 for comparisons) were observed from Week 4 to Week 16. At Week 16, the estimated difference to placebo was 26.2% (p<0.001) with tralokinumab 300 mg Q2W and 25.5% (p<0.001) with tralokinumab 150 mg Q2W.

CDLQI

The change from baseline in CDLQI was larger in both tralokinumab groups compared with the placebo group at each scheduled assessment through the initial treatment period. For tralokinumab 300 mg Q2W, separation to placebo (i.e. p<0.05 for comparisons) was observed from Week 12 to Week 16. For tralokinumab 150 mg Q2W, separation to placebo was observed at Week 16.

The proportion of subjects with a reduction of CDLQI ≥6 from baseline was higher in the tralokinumab 300 mg Q2W and tralokinumab 150 mg Q2W groups than in the placebo group at each scheduled assessment in the initial treatment period. Both separation between tralokinumab 300 mg Q2W and placebo and between tralokinumab 150 mg Q2W and placebo (i.e. p<0.05 for comparisons) were observed from Week 12 to Week 16. At Week 16, the estimated difference to placebo was 23.9% (p<0.001) with tralokinumab 300 mg Q2W and 14.1% (p=0.029) with tralokinumab 150 mg Q2W.

The proportion of subjects with a reduction of CDLQI ≥4 from baseline was higher in the tralokinumab 300 mg Q2W and tralokinumab 150 mg Q2W groups than in the placebo group at each scheduled assessment in the initial treatment period. Separation between tralokinumab 300 mg Q2W and placebo (i.e. p<0.05 for comparisons) was observed from Week 8 to Week 16. Separation between tralokinumab 150 mg Q2W and placebo was observed from Week 12 to Week 16. At Week 16, the estimated difference to placebo was 31.4% (p<0.001) with tralokinumab 300 mg Q2W and 20.7% (p=0.002) with tralokinumab 150 mg Q2W.

Eczema-related Sleep NRS

At Week 16, the change from baseline in Eczema-related Sleep NRS (weekly average) was larger in the tralokinumab 300 mg Q2W and tralokinumab 150 mg Q2W groups compared with the placebo group.

The change from baseline in Eczema-related Sleep NRS (weekly average) was larger in the tralokinumab 300 mg Q2W and tralokinumab 150 mg Q2W groups compared with the placebo group at each scheduled assessment from Week 1 to Week 16. For tralokinumab 300 mg Q2W, separation from placebo (i.e. p<0.05 for comparisons) was observed from Week 9 to Week 16. For tralokinumab 150 mg Q2W, separation from placebo was observed from Week 6 to Week 16.

POEM

The change from baseline in POEM was larger in the tralokinumab 300 mg Q2W and tralokinumab 150 mg Q2W groups compared with the placebo group at each scheduled assessment from in the initial treatment period. For tralokinumab 300 mg Q2W and tralokinumab 150 mg Q2W, separation to placebo (i.e. p<0.05 for comparisons) was observed from Week 2 to Week 16. The proportion of subjects with a reduction of POEM ≥6 was higher in the tralokinumab 300 mg Q2W and tralokinumab 150 mg Q2W groups than in the placebo group at each scheduled assessment in the initial treatment period. Separation between tralokinumab 300 mg Q2W and placebo (i.e. p<0.05 for comparisons) was observed from Week 6 to Week 16. Separation between tralokinumab 150 mg Q2W and placebo was observed from Week 4 to Week 16. At Week 16, the estimated difference to placebo was 36.5% (95% CI: 24.7 to 48.3, p<0.001) with tralokinumab 300 mg Q2W and 28.4% (95% CI: 16.4 to 40.3, p<0.001) with tralokinumab 150 mg Q2W.

Maintenance treatment period

There were 2 maintenance endpoints in the maintenance treatment period:

- IGA of 0/1 at Week 52 among subjects with IGA of 0/1 at Week 16 achieved without rescue treatment from Week 2 to Week 16, after initial randomisation to tralokinumab.

- EASI75 at Week 52 among subjects with EASI75 at Week 16 achieved without rescue treatment from Week 2 to Week 16, after initial randomisation to tralokinumab.

Furthermore, assessments supporting the 2 maintenance endpoints and assessments related to efficacy over time and HRQoL were evaluated in the maintenance treatment period.

The subjects were assigned to maintenance treatment based on their randomised treatment in the initial treatment period and their clinical response at Week 16. The maintenance treatment period included the following groups:

- Week 16 responders initially randomised to tralokinumab 300 mg Q2W were re-randomised to:
  - Tralokinumab 300 mg Q2W (hereafter referred to as tralokinumab 300 mg Q2W/Q2W).
  - Tralokinumab 300 mg Q4W (hereafter referred to as tralokinumab 300 mg Q2W/Q4W).
- Week 16 responders initially randomised to tralokinumab 150 mg Q2W were re-randomised to:
  - Tralokinumab 150 mg Q2W (hereafter referred to as tralokinumab 150 mg Q2W/Q2W).
  - Tralokinumab 150 mg Q4W (hereafter referred to as tralokinumab 150 mg Q2W/Q4W).
- Week 16 responders initially randomised to placebo were assigned to continue on placebo treatment.

Efficacy data from the maintenance treatment period should be interpreted with caution due to the low number of subjects in each treatment group (ranging from 11-14 subjects in the tralokinumab groups).

Panel 34 ***IGA 0/1 at Week 52: maintenance treatment period: subjects in maintenance analysis set with IGA 0/1 at Week 16 achieved without rescue medication***

IGA 0/1 at week 52	Tralokinumab 150 mg Q2W (n= 9)	Tralokinumab 150 mg Q4W (n=10)	Tralokinumab 300 mg Q2W (n= 8)	Tralokinumab 300 mg Q4W (n= 8)
Responders (%) #	6/ 9 (66.7)	6/10 (60.0)	3/ 8 (37.5)	7/ 8 (87.5)
95% CI ##	35.4 to 87.9	31.3 to 83.2	13.7 to 69.4	52.9 to 97.8

CI: Confidence interval. IGA: Investigator's Global Assessment. IGA 0/1: IGA score of clear (0) or almost clear (1). n: Number o subjects in analysis set. Q2W: Every 2 weeks. Q4W: Every 4 weeks.
#) Responders/Total. Subjects who received rescue medication after Week 2 and/or have been permanently discontinued from treatme transferred to open-label treatment considered non-responders. Missing data at Week 52 imputed as non-responders.
##) CI based on Wilson score method.

Panel 35 ***EASI75 at Week 52: maintenance treatment period: subjects in maintenance analysis set with EASI75 at Week 16 achieved without rescue medication***

EASI75 at week 52	Tralokinumab 150 mg Q2W (n=11)	Tralokinumab 150 mg Q4W (n=14)	Tralokinumab 300 mg Q2W (n= 9)	Tralokinumab 300 mg Q4W (n=13)
Responders (%) #	7/11 (63.6)	7/14 (50.0)	4/ 9 (44.4)	7/13 (53.8)
95% CI ##	35.4 to 84.8	26.8 to 73.2	18.9 to 73.3	29.1 to 76.8

CI: Confidence interval. EASI: Eczema Area and Severity Index. EASI75: At least 75% reduction in EASI score. n: Number of subjects in analysis set. Q2W: Every 2 weeks. Q4W: Every 4 weeks.
#) Responders/Total. Subjects who received rescue medication after Week 2 and/or have been permanently discontinued from treatment/ transferred to open-label treatment considered non-responders. Missing data at Week 52 imputed as non-responders.
##) CI based on Wilson score method.

Panel 36 ***EASI75 at Week 52: maintenance treatment period: subjects in FAS assigned to maintenance treatment with IGA 0/1 or EASI75 at Week 16 achieved without rescue***

medication

EASI75 at week 52	Tralokinumab 150 mg Q2W (n=12)	Week 16 Tralokinumab responders* Tralokinumab 150 mg Q4W (n=14)	Tralokinumab 300 mg Q2W (n=11)	Tralokinumab 300 mg Q4W (n=13)	Week 16 Placebo responders* Placebo (n= 6)
Responders (%) #	7/12 (58.3)	7/14 (50.0)	5/11 (45.5)	7/13 (53.8)	3/ 6 (50.0)
95% CI ##	32.0 to 80.7	26.8 to 73.2	21.3 to 72.0	29.1 to 76.8	18.8 to 81.2

CI: Confidence interval. EASI: Eczema Area and Severity Index. EASI75: At least 75% reduction in EASI score. FAS: Full analysis set. IGA: Investigator's Global Assessment. IGA 0/1: IGA score of clear (0) or almost clear (1). n: Number of subjects in analysis set. Q2W: Every 2 weeks. Q4W: Every 4 weeks.
*) Responders/Total. Subjects with IGA 0/1 or EASI 75 at Week 16 achieved without rescue medication.
#) Responders/Total. Subjects who received rescue medication after Week 2 and/or have been permanently discontinued from treatment/ transferred to open-label treatment considered non-responders. Missing data at Week 52 imputed as non-responders.
##) CI based on Wilson score method.

Open-label treatment period (Week 16 to Week 52)

There were no protocol-defined endpoints in the open-label treatment period. However, based on the observation that the majority of subjects transferred to open-label treatment at Week 16, additional efficacy analyses in the open-label treatment period were included in the statistical analysis plan prior to database lock to support the evaluation of the long-term efficacy of tralokinumab.

Subjects were assigned to maintenance treatment or open-label treatment based on their IGA 0/1 and EASI75 responder status at Week 16. 7 subjects were incorrectly transferred to open-label treatment at Week 16 despite achieving IGA 0/1 or EASI75.

Panel 37 ***IGA 0/1 and EASI75 responder status at Week 16 by initial treatment: subjects in FAS transferred to open-label treatment at Week 16***

Responder status at Week 16[a]	Treatment in initial treatment period	Tralokinumab 300 mg Q2W + TCS (n=214)
EASI75 and IGA 0/1 responder	Tralokinumab 150 mg Q2W	1
EASI75 and IGA 0/1 responder	Tralokinumab 300 mg Q2W	1
EASI75 responder only	Tralokinumab 150 mg Q2W	1
EASI75 responder only	Tralokinumab 300 mg Q2W	4
Non-responder	Placebo	79
Non-responder	Tralokinumab 150 mg Q2W	63
Non-responder	Tralokinumab 300 mg Q2W	65

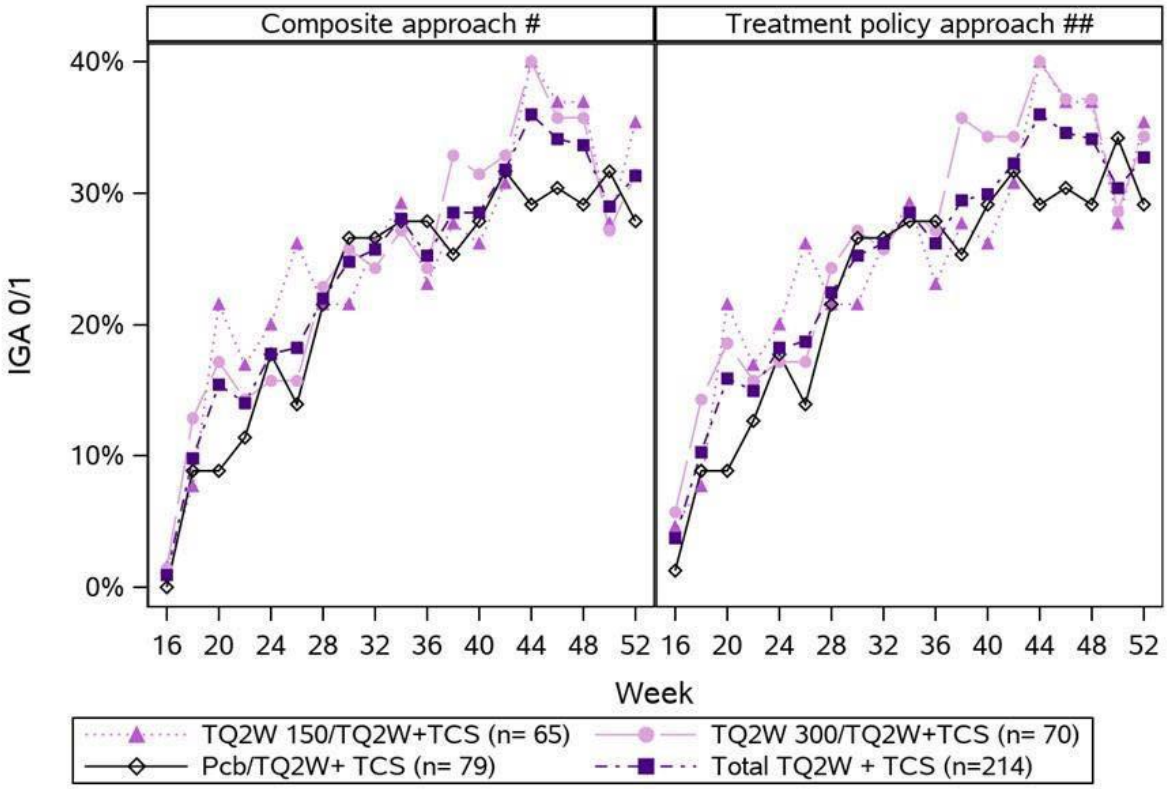
Notes: a = Subjects being responders without rescue medication were wrongly transferred to open-label treatment.

Abbreviations: EASI = Eczema Area and Severity Index; EASI75 = at least 75% reduction in EASI score from baseline; IGA = Investigator's Global Assessment; IGA 0/1 = a score of *clear or almost clear* on the IGA scale; n = number of subjects in analysis set; Q2W = every 2 weeks; TCS = topical corticosteroid.

IGA 0/1

Overall, the proportion of IGA 0/1 responders increased over time in the open-label treatment period, irrespective of treatment in the initial treatment period. Among the 214 subjects who transferred to open-label treatment at Week 16, 31.3% (95% CI: 25.5 to 37.8) achieved IGA 0/1 at Week 52 without use of high potency TCS or systemic treatment (composite approach).

Panel 38 ***IGA 0/1 responders by initial treatment, estimation method, and week in the open-label treatment period: subjects in FAS transferred to open-label treatment at Week 16***



IGA: Investigator's Global Assessment. IGA 0/1: IGA score of clear (0) or almost clear (1). n: Number of subjects in analysis set. Q2W: Every 2 weeks. TCS: topical corticosteroid.
#) Subjects who received rescue during open-label (high potency TCS or systemic treatment) considered non-responders. Subjects who received rescue after Week 2 during initial period (TCI, any TCS or systemic treatment) considered non-responders at Week 16. Subjects with missing data imputed as non-responders.
##) All data used as observed. Subjects with missing data imputed as non-responders.
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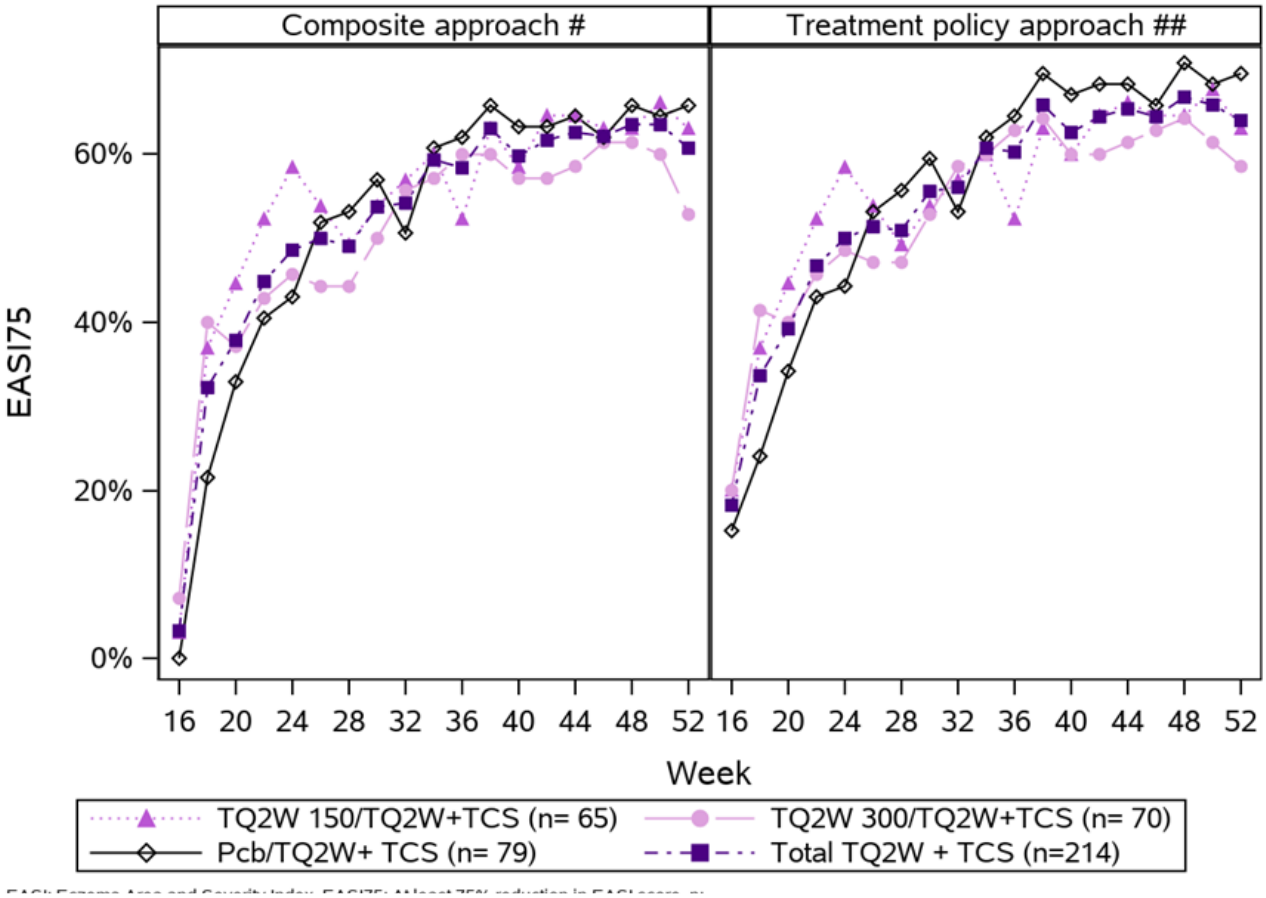
Overall, the proportion of EASI75 responders increased over time in the open-label treatment period, irrespective of treatment in the initial treatment period. Among the 214 subjects who transferred to open-label treatment at Week 16, 60.7% (95% CI: 54.1 to 67.0) achieved EASI75 at Week 52 without use of high potency TCS or systemic treatment.

The proportion of EASI75 responders at Week 52 was higher for subjects initially treated with tralokinumab 150 mg Q2W and placebo compared with subjects initially treated with tralokinumab 300 mg Q2W (composite approach).

Panel 39 ***EASI75 responders by initial treatment, estimation method, and week in the open-label treatment period: subjects in FAS transferred to open-label treatment at Week 16***



Post-hoc analysis of efficacy in the open-label treatment period

In the FAS, 135 subjects initially treated with tralokinumab were transferred to open-label treatment at Week 16.

- 70 subjects transferred from tralokinumab 300 mg Q2W.
- 65 subjects transferred from tralokinumab 150 mg Q2W.

For these subjects, 3 approaches were used to analyse clinical response during open-label treatment:

- Treatment policy approach (pre-defined): All data were used as observed. Subjects with missing data were imputed as non-responders.
- Composite approach (pre-defined): Subjects who used rescue medication during open-label treatment (high-potency TCS or systemic treatment) were considered non-responders. Subjects with missing data were imputed as non-responders.
- **Post-hoc composite approach:** Subjects who used concomitant anti-inflammatory treatments during open-label treatment were considered non-responders. Subjects with missing data were imputed as non-responders

Use of rescue medication (high-potency TCS or systemic treatment) during open-label treatment was low (7.7%; 18/234 subjects) and consisted mostly of topical treatments (primarily higher potency TCS). Therefore, using the treatment policy approach or the composite approach essentially did not affect the

results, and only the treatment policy approach and the post-hoc composite approach are presented below.

Of the subjects randomised to tralokinumab (150 mg or 300 mg) who did not meet the clinical response criteria at Week 16 and who were transferred to the open-label tralokinumab arm, 34.8% (47/135 subjects) achieved IGA 0/1 and 60.7% (82/135 subjects) achieved EASI75 at Week 52, based on the treatment policy approach.

TCS, irrespective of potency, was used by 50.0% of subjects during open-label treatment. To indirectly assess the effect of TCI, any TCS, or systemic treatment during the open-label tralokinumab treatment, IGA 0/1 and EASI75 responder rates were also derived using the post-hoc composite approach. To this end, subjects who used concomitant anti-inflammatory treatments during open-label treatment were considered non-responders. Based on the post-hoc composite approach, 22.2% (30/135 subjects) achieved IGA 0/1 and 34.1% (46/135 subjects) achieved EASI75 at Week 52.

Ancillary analyses

To assess the consistency in response rates for the primary endpoints across different subgroups, the primary endpoints (IGA 0/1 and EASI75) in ECZTRA 6 were summarised by the following subgroups:

- Baseline IGA (moderate, severe).
- Region (North America, Europe, Australia, Asia).
- Race (white, Black or African American, Asian, other).
- Sex.
- Age group (12–14 years and 15–17 years).
- Body weight group (≤60 kg and >60 kg).
- Body weight groups (≤55 kg and >55 kg, ≤60 kg and >60 kg, ≤65 kg and >65 kg, ≤70 kg and >70 kg, ≤80 kg and >80 kg).

IGA 0/1 and EASI75 at Week 16 by baseline IGA

Within each treatment group, the proportion of IGA 0/1 responders was approximately 2.5- to 3-fold higher in subjects with a moderate disease (IGA = 3) at baseline compared to subjects with a severe disease (IGA = 4) at baseline.

Panel 40 ***IGA 0/1 responders at Week 16 by baseline IGA: full analysis set***

IGA 0/1 at Week 16	Tralokinumab 150 mg Q2W (n= 98) Responders(%)*	Tralokinumab 300 mg Q2W (n= 97) Responders(%)*	Placebo (n= 94) Responders(%)*
Primary estimand: Composite**			
Baseline IGA Moderate	17/ 54 (31.5)	12/ 49 (24.5)	3/ 51 (5.9)
Baseline IGA Severe	4/ 44 (9.1)	5/ 48 (10.4)	1/ 43 (2.3)
Tertiary estimand: Treatment policy***			
Baseline IGA Moderate	19/ 54 (35.2)	14/ 49 (28.6)	4/ 51 (7.8)
Baseline IGA Severe	4/ 44 (9.1)	6/ 48 (12.5)	1/ 43 (2.3)

IGA: Investigator's Global Assessment. n: Number of subjects in analysis set. %: Percentage of subjects. Q2W: Every 2 weeks.
*) Responders/Total.
**) Subjects who received rescue medication after Week 2 considered non-responders. Missing values at Week 16 imputed as non-responders.
***) Missing values at Week 16 imputed as non-responders.

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In the corresponding subgroup analysis on EASI75, the proportion of EASI75 responders was approximately 1.5- to 2.5-fold higher in subjects with IGA = 3 at baseline compared with subjects with IGA = 4 at baseline in the tralokinumab groups, and approximately 4-fold higher in subjects with IGA = 3 at baseline compared with subjects with IGA = 4 at baseline in the placebo group.

Panel 41 ***EASI75 responders at Week 16 by baseline IGA: full analysis set***

EASI75 at Week 16	Tralokinumab 150 mg Q2W (n= 98) Responders(%)*	Tralokinumab 300 mg Q2W (n= 97) Responders(%)*	Placebo (n= 94) Responders(%)*
Primary estimand: Composite**			
Baseline IGA Moderate	21/ 54 (38.9)	16/ 49 (32.7)	5/ 51 (9.8)
Baseline IGA Severe	7/ 44 (15.9)	11/ 48 (22.9)	1/ 43 (2.3)
Tertiary estimand: Treatment policy***			
Baseline IGA Moderate	26/ 54 (48.1)	19/ 49 (38.8)	12/ 51 (23.5)
Baseline IGA Severe	13/ 44 (29.5)	17/ 48 (35.4)	7/ 43 (16.3)

EASI: Eczema Area and Severity Index. EASI75: At least 75% reduction in EASI score. n: Number of subjects in analysis set. %: Percentage of subjects. Q2W: Every 2 weeks.
*) Responders/Total.
**) Subjects who received rescue medication after Week 2 considered non-responders. Missing values at Week 16 imputed as non-responders.
***) Missing values at Week 16 imputed as non-responders.

IGA 0/1 and EASI75 at Week 16 by region

Panel 42 ***IGA 0/1 responders at Week 16 by region: full analysis set***

IGA 0/1 at Week 16	Tralokinumab 150 mg Q2W (n= 98) Responders(%)*	Tralokinumab 300 mg Q2W (n= 97) Responders(%)*	Placebo (n= 94) Responders(%)*
Primary estimand: Composite**			
Region Asia	4/ 10 (40.0)	0/ 11 (0.0)	0/ 11 (0.0)
Region Australia	0/ 5 (0.0)	0/ 5 (0.0)	0/ 4 (0.0)
Region Europe	7/ 33 (21.2)	9/ 33 (27.3)	2/ 32 (6.3)
Region North America	10/ 50 (20.0)	8/ 48 (16.7)	2/ 47 (4.3)
Tertiary estimand: Treatment policy***			
Region Asia	5/ 10 (50.0)	0/ 11 (0.0)	0/ 11 (0.0)
Region Australia	0/ 5 (0.0)	1/ 5 (20.0)	0/ 4 (0.0)
Region Europe	8/ 33 (24.2)	10/ 33 (30.3)	2/ 32 (6.3)
Region North America	10/ 50 (20.0)	9/ 48 (18.8)	3/ 47 (6.4)

IGA: Investigator's Global Assessment. n: Number of subjects in analysis set. %: Percentage of subjects. Q2W: Every 2 weeks.
*) Responders/Total.
**) Subjects who received rescue medication after Week 2 considered non-responders. Missing values at Week 16 imputed as non-responders.
***) Missing values at Week 16 imputed as non-responders.

Panel 43 ***EASI75 responders at Week 16 by region: full analysis set***

EASI75 at Week 16	Tralokinumab 150 mg Q2W (n= 98) Responders(%)*	Tralokinumab 300 mg Q2W (n= 97) Responders(%)*	Placebo (n= 94) Responders(%)*
Primary estimand: Composite**			
Region Asia	5/ 10 (50.0)	1/ 11 (9.1)	0/ 11 (0.0)
Region Australia	0/ 5 (0.0)	0/ 5 (0.0)	0/ 4 (0.0)
Region Europe	9/ 33 (27.3)	10/ 33 (30.3)	2/ 32 (6.3)
Region North America	14/ 50 (28.0)	16/ 48 (33.3)	4/ 47 (8.5)
Tertiary estimand: Treatment policy***			
Region Asia	8/ 10 (80.0)	6/ 11 (54.5)	4/ 11 (36.4)
Region Australia	0/ 5 (0.0)	1/ 5 (20.0)	0/ 4 (0.0)
Region Europe	15/ 33 (45.5)	11/ 33 (33.3)	5/ 32 (15.6)
Region North America	16/ 50 (32.0)	18/ 48 (37.5)	10/ 47 (21.3)

EASI: Eczema Area and Severity Index. EASI75: At least 75% reduction in EASI score. n: Number of subjects in analysis set. %: Percentage of subjects. Q2W: Every 2 weeks.
*) Responders/Total.
**) Subjects who received rescue medication after Week 2 considered non-responders. Missing values at Week 16 imputed as non-responders.
***) Missing values at Week 16 imputed as non-responders.

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IGA 0/1 and EASI75 at Week 16 by baseline body weight

There was no meaningful association between tralokinumab dose, body weight, and IGA 0/1 or EASI75 response rates at Week 16. For both IGA 0/1 and EASI75, response rates were higher in subjects with a body weight ≤60 kg in the tralokinumab 300 mg Q2W group and higher in subjects with a body weight >60 kg in the tralokinumab 150 mg Q2W group.

Panel 44 ***IGA 0/1 responders at Week 16 by baseline body weight (≤60 kg vs. >60 kg): full analysis set***

IGA 0/1 at Week 16	Tralokinumab 150 mg Q2W (n= 98) Responders (%)*	Tralokinumab 300 mg Q2W (n= 97) Responders (%)*	Placebo (n= 94) Responders (%)*
Primary estimand: Composite**			
Weight group <=60	8/ 51 (15.7)	11/ 53 (20.8)	3/ 50 (6.0)
Weight group >60	13/ 47 (27.7)	6/ 44 (13.6)	1/ 44 (2.3)
Tertiary estimand: Treatment policy***			
Weight group <=60	9/ 51 (17.6)	14/ 53 (26.4)	3/ 50 (6.0)
Weight group >60	14/ 47 (29.8)	6/ 44 (13.6)	2/ 44 (4.5)

IGA: Investigator's Global Assessment. IGA 0/1: IGA score of clear (0) or almost clear (1). n: Number of subjects in analysis set. %: Percentage of subjects. Q2W: Every 2 weeks.
*) Responders/Total.
**) Subjects who received rescue medication after Week 2 considered non-responders. Missing values at Week 16 imputed as non-responders.
***) Missing values at Week 16 imputed as non-responders.

Panel 45 ***EASI75 responders at Week 16 by baseline body weight (≤60 kg vs. >60 kg): full analysis set***

EASI75 at Week 16	Tralokinumab 150 mg Q2W (n= 98) Responders (%)*	Tralokinumab 300 mg Q2W (n= 97) Responders (%)*	Placebo (n= 94) Responders (%)*
Primary estimand: Composite**			
Weight group <=60	9/ 51 (17.6)	17/ 53 (32.1)	4/ 50 (8.0)
Weight group >60	19/ 47 (40.4)	10/ 44 (22.7)	2/ 44 (4.5)
Tertiary estimand: Treatment policy***			
Weight group <=60	16/ 51 (31.4)	24/ 53 (45.3)	9/ 50 (18.0)
Weight group >60	23/ 47 (48.9)	12/ 44 (27.3)	10/ 44 (22.7)

EASI: Eczema Area and Severity Index. EASI75: At least 75% reduction in EASI score. n: Number of subjects in analysis set. %: Percentage of subjects. Q2W: Every 2 weeks.
*) Responders/Total.
**) Subjects who received rescue medication after Week 2 considered non-responders. Missing values at Week 16 imputed as non-responders.
***) Missing values at Week 16 imputed as non-responders.

IGA 0/1 and EASI75 at Week 16 by baseline age group

For both IGA 0/1 and EASI75, there was no consistent pattern in the proportion of responders across baseline age subgroups between the treatment groups. In the tralokinumab 300 mg Q2W group, the response rates for both endpoints were similar between the younger and older subjects; in the tralokinumab 150 mg Q2W group, the response rates were higher in the younger subjects; and in the placebo group, the response rates were higher in the older subjects.

Panel 46 ***IGA 0/1 responders at Week 16 by baseline age group (12-14 years vs. 15-17 years): full analysis set***

IGA 0/1 at Week 16	Tralokinumab 150 mg Q2W (n= 98) Responders(%)*	Tralokinumab 300 mg Q2W (n= 97) Responders(%)*	Placebo (n= 94) Responders(%)*
Primary estimand: Composite**			
Age group 12-14	11/ 37 (29.7)	8/ 45 (17.8)	0/ 49 (0.0)
Age group 15-17	10/ 61 (16.4)	9/ 52 (17.3)	4/ 45 (8.9)
Tertiary estimand: Treatment policy***			
Age group 12-14	12/ 37 (32.4)	9/ 45 (20.0)	0/ 49 (0.0)
Age group 15-17	11/ 61 (18.0)	11/ 52 (21.2)	5/ 45 (11.1)

IGA: Investigator's Global Assessment. n: Number of subjects in analysis set. %: Percentage of subjects. Q2W: Every 2 weeks.
*) Responders/Total.
**) Subjects who received rescue medication after Week 2 considered non-responders. Missing values at Week 16 imputed as non-responders.
***) Missing values at Week 16 imputed as non-responders.

Panel 47 ***EASI75 responders at Week 16 by baseline age group (12-14 years vs. 15-17 years): full analysis set***

EASI75 at Week 16	Tralokinumab 150 mg Q2W (n= 98) Responders(%)*	Tralokinumab 300 mg Q2W (n= 97) Responders(%)*	Placebo (n= 94) Responders(%)*
Primary estimand: Composite**			
Age group 12-14	14/ 37 (37.8)	12/ 45 (26.7)	1/ 49 (2.0)
Age group 15-17	14/ 61 (23.0)	15/ 52 (28.8)	5/ 45 (11.1)
Tertiary estimand: Treatment policy***			
Age group 12-14	18/ 37 (48.6)	16/ 45 (35.6)	7/ 49 (14.3)
Age group 15-17	21/ 61 (34.4)	20/ 52 (38.5)	12/ 45 (26.7)

EASI: Eczema Area and Severity Index. EASI75: At least 75% reduction in EASI score. n: Number of subjects in analysis set. %: Percentage of subjects. Q2W: Every 2 weeks.
*) Responders/Total.
**) Subjects who received rescue medication after Week 2 considered non-responders. Missing values at Week 16 imputed as non-responders.
***) Missing values at Week 16 imputed as non-responders.

Table 2 ***EASI75 at Week 16 by subgroup, logistic regression analysis: full analysis set***

EASI75 at Week 16	p-value*
treatment x baseline IGA	0.4478
treatment x region	0.1637
treatment x sex	0.1243
treatment x age group at baseline	0.0631
treatment x weight group at baseline <=50 vs >50	0.4249
treatment x weight group at baseline <=60 vs >60	0.0256
treatment x weight group at baseline <=70 vs >70	0.5110
treatment x race**	0.9476

EASI: Eczema Area and Severity Index. EASI75: At least 75% reduction in EASI score. IGA: Investigator's Global Assessment.
*) Interaction test between treatment and subgroup using a logistic regression model with the factors region - except when region is a subgroup, baseline IGA - except when baseline IGA is a subgroup, treatment, subgroup, treatment*subgroup interaction. Regions Australia and Europe are collapsed in the analyses due to quasi-complete separation (i.e. no responders observed for region Australia).
**) Other, Native Hawaiian or Other Pacific Islander and American Indian or Alaska Native collapsed into Other due to sparse data.

Table 3 ***IGA 0/1 at Week 16 by subgroup, logistic regression analysis: full analysis set***

IGA 0/1 at Week 16	p-value*
treatment x baseline IGA	0.8121
treatment x region	0.0817
treatment x sex	0.0719
treatment x age group at baseline	0.0195
treatment x weight group at baseline <=50 vs >50	0.6144
treatment x weight group at baseline <=60 vs >60	0.1509
treatment x weight group at baseline <=70 vs >70	0.7748
treatment x race**	

IGA: Investigator's Global Assessment. IGA 0/1: IGA score of clear (0) or almost clear (1).
*) Interaction test between treatment and subgroup using a logistic regression model with the factors region - except when region is a subgroup, baseline IGA - except when baseline IGA is a subgroup, treatment, subgroup, treatment*subgroup interaction. Regions Australia and Europe are collapsed in the analyses due to quasi-complete separation (i.e. no responders observed for region Australia).
**) Analysis is omitted since the specified model did not converge due to sparse data.

Summary of main study

The following tables summarise the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 4 ***Summary of Efficacy for trial ECZTRA 6***

<table>
<tr><td colspan="5"><u>Title:</u> Tralokinumab monotherapy for adolescent subjects with moderate-to-severe atopic dermatitis ECZTRA 6 (ECZema TRAlokinumab trial no. 6)</td></tr>
<tr><td>Study identifier</td><td colspan="4">LP0162-1334</td></tr>
<tr><td rowspan="2">Design</td><td colspan="4">Randomised, double-blind, placebo-controlled trials in adolescent subjects with moderate-to-severe AD</td></tr>
<tr><td colspan="2">Duration of main phase:
Duration of Run-in phase:
Duration of Extension phase:</td><td colspan="2">16 weeks
2-6 weeks
36 weeks</td></tr>
<tr><td>Hypothesis</td><td colspan="4">Superiority</td></tr>
<tr><td rowspan="2">Treatments groups</td><td colspan="2">Tralokinumab</td><td colspan="2">300mg Q2W
150mgQ2W</td></tr>
<tr><td colspan="2">Placebo</td><td colspan="2">Q2W</td></tr>
<tr><td rowspan="3">Endpoints and definitions</td><td>Primary endpoint</td><td>IGA 0/1</td><td colspan="2">IGA score of 0 (clear) or 1 (almost clear) at Week 16.</td></tr>
<tr><td>Primary endpoint</td><td>EASI-75</td><td colspan="2">EASI75 at Week 16</td></tr>
<tr><td>Secondary endpoint</td><td>Adolescent Worst Pruritus NRS</td><td colspan="2">Reduction of Adolescent Worst Pruritus NRS (weekly average) of at least 4 from baseline to Week 16</td></tr>
<tr><td colspan="5"><u>Results and Analysis</u> Data lock point: 12-May-2021</td></tr>
<tr><td>Analysis description</td><td colspan="4">Primary Analysis</td></tr>
<tr><td>Analysis population and time point description</td><td colspan="4">Primary estimand ‘composite’:
Treatment difference in response rates of IGA 0/1 and EASI75 after 16 weeks achieved without rescue treatment from Week 2 to Week 16, regardless of treatment discontinuation.</td></tr>
<tr><td rowspan="4">Descriptive statistics and estimate variability</td><td>Treatment group</td><td colspan="2">Tralokinumab 150mgQ2W</td><td>Placebo</td></tr>
<tr><td>Number of subjects</td><td colspan="2">98</td><td>94</td></tr>
<tr><td>IGA 0/1 (%)</td><td colspan="2">21/98 (21.4%)</td><td>4/94 (4.3%)</td></tr>
<tr><td>Difference (%)
95% CI
P-value</td><td colspan="3">150mg Q2W
Difference = 17.5%, 95% CI= (8.4; 26.6)
P-value <0.001</td></tr>
</table>

	Treatment group	Tralokinumab 300mgQ2W	Placebo
	Number of subjects	97	94
	IGA 0/1 (%)	17/97(17.5%)	4/94 (4.3%)
	Difference (%) 95% CI P-value	**300 mg Q2W** Difference = 13.8%, 95% CI= (5.3; 22.3) P-value =0.002	
	Treatment group	Tralokinumab 150mgQ2W	Placebo
	EASI-75 (%)	28/98 (28.6%)	6/94 (6.4%)
	Difference (%) 95% CI P-value	**150mg Q2W** Difference = 22.5%, 95% CI= (12.4; 32.6) P-value <0.001	
	Treatment group	Tralokinumab 300mgQ2W	Placebo
	EASI-75 (%)	27/97(27.8%)	6/94 (6.4%)
	Difference (%) 95% CI P-value	**300 mg Q2W** Difference = 22.0%, 95% CI= (12.0; 32.0) P-value =<0.001	
	Treatment group	Tralokinumab 150mgQ2W	Placebo
	Adolescent Pruritus NRS Reduction ≥ 4	22/95 (23.2%)	3/90 (3.3%)
	Difference (%) 95% CI P-value	**150mg Q2W** Difference = 19.9%, 95% CI= (10.6; 29.2) P-value <0.001	
	Treatment group	Tralokinumab 300mgQ2W	Placebo
	Adolescent Pruritus NRS Reduction ≥ 4	24/96(25.0%)	3/90 (3.3%)
	Difference (%) 95% CI P-value	**300 mg Q2W** Difference = 21.7%, 95% CI= (12.3; 31.1) P-value =<0.001	
Notes	The results of only one of the secondary endpoints (Adolescent Worst Pruritus NRS) is mentioned in this table. Other secondary and tertiary endpoints resulted in same pattern.		

Analysis performed across trials (pooled analyses and meta-analysis)

Comparison of demographics and baseline characteristics of subject enrolled to ECZTRA 6 versus ECZTRA 1 and 2.

The demographics and key baseline characteristics in ECZTRA 6 were well balanced between treatment groups. The data were overall consistent with those in the monotherapy pool in adults, except for the expected differences in age and body weight between adolescents and adults, as well as a minor difference between adolescents and adults in the distribution of subjects between North America and Europe.

Baseline disease characteristics

The baseline disease characteristics in ECZTRA 6 were also well balanced between treatment groups and consistent with those in the monotherapy pool in adults. It should be noted that results from the CDLQI and DLQI questionnaires cannot be directly compared due to differences in the items to be scored. However, in both adolescents and adults, median baseline CDLQI/DLQI scores were within the category of 'very large effect' on subjects' health-related quality of life.

Panel 48 ***Baseline disease characteristics in ECZTRA 6 and monotherapy pool (ECZTRA 1+2)***

	ECZTRA 6 (adolescents)			ECZTRA 1+2 (adults)	
	Tralokinumab 150 mg Q2W (N=98)	Tralokinumab 300 mg Q2W (N=97)	Placebo (N=94)	Tralokinumab 300 mg Q2W (N=1196)	Placebo (N=400)
BSA (%)affected by atopic dermatitis					
n	98	97	94	1196	399
Mean(SD)	52.4 (22.6)	49.6 (23.3)	51.4 (23.9)	52.7 (24.8)	53.6 (25.3)
Median	49.0	44.0	52.0	50.0	51.0
Min;Max	11;100	16;100	10;100	10;100	10;100
IGA					
n	98	97	94	1196	400
Moderate (3)	54 (55.1%)	49 (50.5%)	51 (54.3%)	601 (50.3%)	195 (48.8%)
Severe (4)	44 (44.9%)	48 (49.5%)	43 (45.7%)	591 (49.4%)	203 (50.8%)
Missing	0	0	0	4 (0.3%)	2 (0.5%)
EASI score					
n	98	97	94	1192	398
Mean(SD)	32.05 (12.94)	31.76 (13.91)	31.21 (14.47)	32.2 (14.0)	32.7 (13.9)
Median	28.90	28.00	27.15	28.2	29.8
Min;Max	16.0;68.4	16.0;72.0	16.0;68.4	15.4;72.0	16.0;72.0
SCORAD score					
n	98	97	94	1192	398
Mean(SD)	67.66 (14.38)	68.31 (13.71)	67.36 (14.91)	70.2 (13.2)	71.1 (12.4)
Median	65.00	68.30	66.65	69.3	70.7
Min;Max	41.8;103.0	36.9;100.4	30.6;100.7	19.9;102.8	38.8;103.0
Adolescent Worst Pruritus NRS / Worst Daily Pruritus NRS (weekly average)					
n	96	96	92	1182	395
Mean(SD)	7.49 (1.58)	7.83 (1.53)	7.49 (1.65)	7.8 (1.5)	7.8 (1.4)
Median	7.54	8.14	7.62	7.9	8.0
Min;Max	1.4;10.0	4.1;10.0	2.1;10.0	2.3;10.0	3.0;10.0
CDLQI / DLQI score					
n	95	94	89	1178	394
Mean(SD)	12.93 (6.27)	13.40 (7.26)	13.34 (6.04)	17.3 (7.1)	17.5 (7.0)
Median	13.00	13.00	13.00	17.0	17.0
Min;Max	2.0;27.0	0.0;29.0	1.0;29.0	1.0;30.0	2.0;30.0
POEM score					
n	95	94	87	1175	394
Mean(SD)	20.3 (5.8)	20.1 (5.8)	20.8 (5.6)	22.8 (5.0)	23.0 (4.8)
Median	22.0	21.0	21.0	24.0	24.0
Min;Max	4;28	6;28	4;28	3.0;28.0	0.0;28.0
HADS total score					
n	95	94	89	1174	394
Mean(SD)	10.2 (7.3)	11.6 (7.6)	11.4 (7.3)	12.7 (7.7)	13.1 (7.5)
Median	9.0	10.0	10.0	11.0	12.0
Min;Max	0;32	0;36	0;33	0;38	0;39

Comparison of efficacy results in adolescents and adults

The difference between tralokinumab and placebo was statistically significant for all the primary and confirmatory secondary endpoints, and the results for tralokinumab in adolescents resembled those seen in the adult population.

For IGA 0/1, EASI75, change in SCORAD, and reduction of Pruritus NRS ≥4 at Week 16, the placebo response was lower in ECZTRA 6 than in the adult monotherapy pool, and thus the treatment difference to placebo was higher in adolescents than in adults.

With respect to tralokinumab 150 mg versus 300 mg in ECZTRA 6, the responder rates for the primary endpoints were similar (including IGA 0/1 at Week 16, which is considered similar for tralokinumab 150 mg and 300 mg, given that the IGA scale is relatively coarse and the IGA 0/1 response criterion is static).

Panel 49 ***Primary analysis of multiplicity-adjusted primary and secondary endpoints at Week 16 in ECZTRA 6 and monotherapy pool (ECZTRA 1+2)***

Endpoint	ECZTRA 6 (adolescents)			ECZTRA 1+2 (adults)	
	Tralokinumab 150 mg Q2W (N=98)	Tralokinumab 300 mg Q2W (N=97)	Placebo (N=94)	Tralokinumab 300 mg Q2W (N=1192)	Placebo (N=398)
Primary endpoints					
IGA 0/1 at Week 16[a]	21.4% 17.5% (8.4 to 26.6) <0.001	17.5% 13.8% (5.3 to 22.3) 0.002	4.3%	19.0% 9.8% (6.4 to 13.3) <0.001	9.0%
EASI75 at Week 16[a]	28.6% 22.5% (12.4 to 32.6) <0.001	27.8% 22.0% (12.0 to 32.0) <0.001	6.4%	29.0% 16.9% (12.8 to 20.9) <0.001	12.1%
Secondary endpoints					
Change in SCORAD from baseline to Week 16[b]	-27.5 -18.0 (-25.6 to -10.4) <0.001	-29.1 -19.7 (-27.1 to -12.2) <0.001	-9.5	-26.5 -12.3 (-15.1 to -9.5) <0.001	-14.3
Reduction of Pruritus NRS of ≥4 from baseline to Week 16[a, c]	23.2% 19.9% (10.6 to 29.2) <0.001	25.0% 21.7% (12.3 to 31.1) <0.001	3.3%	22.5% 12.6% (8.9 to 16.4) <0.001	9.9%
Change in CDLQI / DLQI from baseline to Week 16[b]	-6.1 -2.0 (-3.9 to -0.1) 0.040	-6.7 -2.6 (-4.5 to -0.7) 0.007	-4.1	-8.0 -3.0 (-3.9 to -2.0) <0.001	-5.0

Panel 50 ***Analysis of selected additional secondary and other endpoints at Week 16 in ECZTRA 6 and monotherapy pool (ECZTRA 1+2)***

Endpoint / assessment	ECZTRA 6 (adolescents)			ECZTRA 1+2 (adults)	
	Tralokinumab 150 mg Q2W (N=98)	Tralokinumab 300 mg Q2W (N=97)	Placebo (N=94)	Tralokinumab 300 mg Q2W (N=1192)	Placebo (N=398)
AD severity and extent					
EASI50 at Week 16[a]	45.9%	51.5%	13.8%	45.7%	20.9%
	32.4% (20.6 to 44.1) <0.001	38.5% (26.8 to 50.2) <0.001		24.7% (19.9 to 29.5) <0.001	
EASI90 at Week 16[a]	19.4%	17.5%	4.3%	16.4%	4.8%
	15.3% (6.5 to 24.1) <0.001	13.7% (5.2 to 22.2) 0.002		11.5% (8.6 to 14.4) <0.001	
Patient-reported outcomes					
Change in POEM from baseline to Week 16[b]	-7.8	-8.4	-2.4	-8.2	-3.4
	-5.4 (-7.9 to -3.0) <0.001	-6.0 (-8.4 to -3.6) <0.001		-4.8 (-5.8 to -3.8) <0.001	
Change in Eczema-related Sleep NRS from baseline to Week 16[b]	-2.9	-3.1	-1.8	-2.8	-1.7
	-1.1 (-2.0 to -0.2) 0.015	-1.3 (-2.2 to -0.4) 0.005		-1.1 (-1.4 to -0.7) <0.001	
Change in HADS total score from baseline to Week 16[b]	-1.8	-4.4	-2.1	-2.8	-1.6
	0.3 (-1.8 to 2.3) 0.81	-2.3 (-4.3 to -0.3) 0.023		-1.2 (-1.9 to -0.4) 0.003	
Reduction of POEM of ≥6 (adolescents) or of ≥4 (adults) from baseline to Week 16[a,c]	≥6: 38.7%	≥6: 46.8%	≥6: 10.5%	≥4: 48.7%	≥4: 20.1%
	28.4% (16.4 to 40.3) <0.001	36.5% (24.7 to 48.3) <0.001		28.6% (23.8 to 33.4) <0.001	
Reduction of CDLQI (of ≥6) / DLQI (of ≥4) from baseline to Week 16[a,c]	≥6: 31.0%	≥6: 39.5%	≥6: 15.9%	≥4: 50.5%	≥4: 29.4%
	14.1% (1.8 to 26.5) 0.029	23.9% (11.0 to 36.7) <0.001		21.0% (15.7 to 26.4) <0.001	

Notes: Analysis set: full analysis set; Results are responders without any use of rescue medication after Week 2 (in ECZTRA 6) or after baseline (in ECZTRA 1+2) (%) or adjusted mean change (white area), treatment difference versus placebo, 95% CI, and p-value (grey area). **a** = Analysed using composite strategy; **b** = Analysed using hypothetical strategy; **c** = Not defined as endpoints in ECZTRA 6 but pre-specified in the SAP; reduction of ≥6 not assessed in ECZTRA 1+2.

Abbreviations: AD = atopic dermatitis; CDLQI = Children's Dermatology Life Quality Index (assessed in ECZTRA 6); DLQI = Dermatology Life Quality Index (assessed in ECZTRA 1+2); EASI50 / 90 = at least 50 / 90% reduction in Eczema Area and Severity Index score; HADS = Hospital Anxiety and Depression Scale; N = number of subjects in analysis set; POEM = Patient-Oriented Eczema Measure; Q2W = every 2 weeks.

Maintenance treatment period

The maintenance of response for both IGA 0/1 and EASI75 in ECZTRA 6 was in accordance with previous findings in the adult monotherapy pool. Direct comparison of the results in adolescents with those in adults, as well as comparison between the different maintenance treatment regimens in ECZTRA 6, should be interpreted with caution due to the low number of subjects on each maintenance treatment regimen in ECZTRA 6.

Panel 51 ***Clinical response at Week 52 among subjects who met the clinical response criteria on tralokinumab at Week 16 without any rescue medication in ECZTRA 6 and monotherapy pool (ECZTRA 1+2)***

Endpoint	ECZTRA 6 (adolescents)				ECZTRA 1+2 (adults)	
	Tralokinumab 150 mg Q2W	Tralokinumab 150 mg Q4W	Tralokinumab 300 mg Q2W	Tralokinumab 300 mg Q4W	Tralokinumab 300 mg Q2W	Tralokinumab 300 mg Q4W
IGA 0/1 responders at Week 52 among subjects with IGA 0/1 at Week 16						
N	9	10	8	8	93	85
n (%)	6 (66.7)	6 (60.0)	3 (37.5)	7 (87.5)	52 (55.9)	36 (42.4)
EASI75 responders at Week 52 among subjects with EASI75 at Week 16						
N	11	14	9	13	124	131
n (%)	7 (63.6)	7 (50.0)	4 (44.4)	7 (53.8)	71 (57.3)	66 (50.4)

Notes: Analysis set: maintenance analysis set; Subjects who received rescue medication after Week 2 (in ECZTRA 6) or after baseline (in ECZTRA 1+2), or have been permanently discontinued from treatment/transferred to open-label treatment were considered as non-responders. Missing data at Week 52 were imputed as non-responders.

Abbreviations: EASI75 = at least 75% reduction in Eczema Area and Severity Index score; IGA 0/1 = Investigator's Global Assessment response of 0 (clear) or 1 (almost clear); N = number of subjects in analysis set; n = number of responders; Q2W = every 2 weeks; Q4W = every 4 weeks.

Source: Modified from M5.3.5.1 ECZTRA 6 CTR Tables 6.173 and 6.175; initial M2.7.3 Panel 50.

2.4.3. Discussion on clinical efficacy

The purpose of this submission was to provide data supporting the use of tralokinumab in adolescents (12–17 years) with AD. In relation to supportive studies, the ECZTEND study is still ongoing and therefore only information on exposure, SAEs, and AEs leading to permanent discontinuation of IMP for the adolescent subjects transferred from ECZTRA 6 was available.

Design and conduct of clinical studies

The ECZTRA 6 study consisted of a screening period (2 to 6 weeks), an initial treatment period of 16 weeks and a maintenance treatment period of 36 weeks in subjects who obtained a clinical response at Week 16, and a concurrent open-label treatment period of up to 36 weeks in subjects who did not achieve the protocol-defined clinical response at Week 16 or who received rescue treatment from Week 2 to Week 16. In this study performed in adolescents two doses were tested during the initial treatment period i.e the dose which was investigated in adults i.e tralokinumab 600 mg at baseline, then tralokinumab 300 mg Q2W or the dose reduced by half as compared to the adults dose i.e tralokinumab 300 mg at baseline, then tralokinumab 150 mg Q2W.

At Week 16, subjects with a clinical response (achieved without use of rescue treatment from Week 2 to Week 16) were re-randomised and included in the maintenance treatment period. During the maintenance treatment period four doses were tested (300 mg Q2W, 300 mg Q4W, 150 mg Q2W, 150 mg Q4W). Two

of these 4 doses were investigated in adults and two remaining were lower as compared to those investigated in adults.

Although additional doses were tested in adolescents the applicant is not proposing to change posology for adolescents as compared to adults. The SmPC states:

The recommended dose of tralokinumab for adult and adolescent patients 12 years and older patients is an initial dose of 600 mg (four 150 mg injections) followed by 300 mg (two 150 mg injections) administered every other week as subcutaneous injection.

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.

Eligibility criteria

ECZTRA 6 enrolled adolescents (aged 12 to 17 years) with body weight at baseline ≥30.0 kg.

Other eligibility criteria in ECZTRA 6 were similar to those used in ECZTRA 1 and 2 studies.

Patients selected in ECZTRA 6 study had at least 1 year diagnosis of AD as defined by the Hanifin and Rajka (1980) criteria for AD. Active disease severity was rated to moderate-to-severe by baseline AD severity scores of IGA ≥3, EASI ≥12 (at screening) and EASI ≥16 (at baseline) and 10% BSA involvement with AD. In addition, the Adolescent Pruritus NRS average score had to be ≥4 during one week prior to baseline.

However, there were some differences in relation to a history of topical corticosteroid use prior to enrolment. All enrolled patients were required to have a history of topical corticosteroid use (Europe: Class 3 or higher; US: Class 4 or lower) and/or topical corticosteroid treatment failure or subjects for whom these topical AD treatments are medically inadvisable. This inclusion criteria seemed to be wider as compared to the criteria used in ECZTRA 1 and 2 studies. In ECZTRA 1 and 2 studies all enrolled subjects were required to have an inadequate response to treatment with 'TCS of medium to higher potency' lasting at least 28 days (or the maximum recommended treatment duration in the product prescribing information if this was less than 28 days) within 1 year prior to the screening visit.
Therefore, the applicant was asked to discuss differences in relation to the inclusion criteria as compared to ECZTRA 1 and 2 studies.

The applicant clarified that a history of TCS use only was not sufficient requirement for enrolling to ECZTRA 6 study, as subjects had to have a history of treatment failure with TCS (defined as either inadequate response or intolerance). In addition, the applicant clarified that the potency of previously used TCS required to meet these inclusion criteria were the same in ECZTRA 1, 2, and 6. Therefore, the inclusion criteria used in ECZTRA 6 were not significantly different as compared to those used in the pivotal studies used in the original MAA.

Primary endpoints

The primary endpoints of this study were EASI-75 at week 16 and IGA 0 or 1 at week 16. These primary endpoints are considered adequate and in line with the CHMP recommendation.

There were a number of secondary endpoints in the study; Endpoints under multiplicity adjustment for the initial treatment period were reduction of Adolescent Worst Pruritus NRS (weekly average) of at least 4 from baseline to Week 16, change in SCORAD from baseline to Week 16 and Change in CDLQI score from baseline to Week 16.

In the study there was hierarchical testing with the results for the 300 mg dose tested first (primary and confirmatory secondary endpoints) before the results for the 150 mg dose was tested.

Endpoints for the maintenance treatment period were not under multiplicity adjustment. The main endpoints for this period were:

- IGA of 0/1 at Week 52 among subjects with IGA of 0/1 at Week 16 achieved without rescue treatment from Week 2 to Week 16, after initial randomisation to tralokinumab
- EASI75 at Week 52 among subjects with EASI75 at Week 16 achieved without rescue treatment from Week 2 to Week 16, after initial randomisation to tralokinumab.

Efficacy data and additional analyses

In study ECZTRA 6 a total of 347 patients were screened, of whom 301 were enrolled into the study and randomized (101 subjects randomised to tralokinumab 300 mg Q2W, 100 subjects randomised to tralokinumab 150 mg Q2W and 100 subjects randomised to placebo).

9 of the randomised subjects were enrolled at two investigational sites with GCP non-compliance issues (3 subjects randomised to tralokinumab 300 mg Q2W, 1 subject randomised to tralokinumab 150 mg Q2W, and 5 subjects randomised to placebo). These subjects were excluded from the FAS as in 340 or 341 major GCP issues were identified.

In total, 273 subjects (90.7% of all randomised subjects) completed Week 16 on treatment. Of these 273 subjects, 94 subjects were treated with tralokinumab 300 mg Q2W, 93 subjects were treated with tralokinumab 150 mg Q2W, and 86 subjects received placebo.

56 of the subjects in the FAS were assigned to maintenance treatment.

- 24 subjects initially randomised to tralokinumab 300 mg Q2W were re-randomised 1:1 to tralokinumab 300 mg Q2W or tralokinumab 300 mg Q4W.
- 26 subjects initially randomised to tralokinumab 150 mg Q2W were re-randomised 1:1 to tralokinumab 150 mg Q2W or tralokinumab 150 mg Q4W.
- 6 subjects initially randomised to placebo were assigned to continue placebo treatment.

A total of 220 subjects (214 subjects included in the FAS and 6 subjects randomised at investigational sites with GCP non-compliance issues) were transferred to open-label treatment at Week 16. Additionally, 22 subjects (20 subjects included in the FAS and 2 subjects randomised at investigational sites with GCP non-compliance issues) transferred to open-label treatment after Week 16.

Demographic and other baseline characteristics

The overall mean age at baseline was 14.6 years (ranging from 12 to 17). More than 51% of patients enrolled to the study were male, and the majority of patients enrolled were white (56.7%). Asian subjects accounted for about 24 % of population, whereas black subjects accounted for 11% of subjects.

Apart from a higher percentage of subjects with severe disease in the tralokinumab 300 mg Q2W group (49.5%) compared with the tralokinumab 150 mg Q2W (44.9%) and placebo (45.7%) groups, the baseline disease severity was well balanced between treatment groups in the initial treatment period. The mean BSA at the baseline was 51%, the mean EASI score was around 32.

As required by the trial protocol all patients enrolled to the study had used topical corticosteroids prior to recruitment. In addition, a significant percentage of patients had previously used systemic steroids (45%) and topical Calcineurin inhibitors (59%). Systemic immunosuppressants (including cyclosporine, methotrexate, mycophenolate and Azathioprine) were used by 21% of subjects.

It is noted that to the maintenance treatment period a significantly lower proportion of patients with a severe disease were enrolled as compared to patients who entered the initial treatment period.

Rescue therapy

If medically necessary (i.e. to control intolerable AD symptoms), rescue treatment for AD could be provided to trial subjects at the discretion of the investigator. For analysis of the primary estimand for the primary endpoints, subjects who received rescue treatment from Week 2 to Week 16 were considered as non-responders. Subjects had to use an emollient twice daily throughout the trial. During the initial treatment period and maintenance treatment period use of TCS of any WHO class and other AD therapies were classified as a rescue treatment.

Overall, during the initial treatment period recue medications were used more frequently in the placebo group (56.4%) as compared to the tralokinumab groups (33.7% for 150 mg Q2W and 29.9% for 300mg Q2W). The vast majority of rescue medication used in this pivotal trial were topical corticosteroids and the use of rescue medication was higher in subjects with severe disease at the baseline. There was a significant variation in the use of rescue medication between the regions as well as between treatment groups. Variability in the use of rescue medications between the regions was also observed in the studies provided in the support of the original MAA.

The definition of rescue medication in the open-label treatment period was different from the initial and maintenance treatment periods as use of mild to moderate TCS was allowed. Use of rescue medication was low in the open-label treatment period (7.7% subjects).

Primary endpoints results

The primary endpoints i.e the proportion of patients with EASI-75 at week 16 and the proportion of patients with IGA 0 or 1 at week 16 for both doses investigated in the initial treatment period were met.

In the primary analysis of the primary estimand, the proportion of patients with IGA 0 or 1 at week 16 was higher in both tralokinumab treatment groups (21.4% and 17.5% for 150 mg Q2W group and 300 mg Q2W group, respectively) than in the placebo group (4.3%) with $p<0.001$ for 150 mg Q2W group and 0.002 for 300 mg Q2W group.

Very similar results were observed for sensitivity analysis 1 of the primary estimand.

Also the proportion of patients with EASI-75 at week 16 was higher in the tralokinumab groups (28.6% and 27.8 % for 150 mg Q2W group and 300 mg Q2W group, respectively) than in the placebo group (6.4%). The observed differences were statistically significant ($p<0.0001$ for each).

For IGA 0/1 and EASI75, the placebo response was lower in ECZTRA 6 than in the adult monotherapy pool, and thus the treatment difference to placebo was slightly higher in adolescents than in adults.

In ECZTRA 6, for IGA 0/1 the estimated difference to placebo was 17.5% ($p<0.001$) with tralokinumab 150 mg Q2W and 13.8% ($p=0.002$) with tralokinumab 300 mg Q2W. By comparison, ECZTRA 1+2 for IGA 0/1 the estimated difference to placebo was 9.8 % ($p<0.001$).

In ECZTRA 6, for EASI-75 the estimated difference to placebo was 22.5 % ($p<0.001$) with tralokinumab 150 mg Q2W and 22.2% ($p<0.001$) with tralokinumab 300 mg Q2W. By comparison, ECZTRA 1+2 for EASI-75 the estimated difference to placebo was 16.9 % ($p<0.001$).

In respect to the results of the primary endpoints, there were no significant differences for two doses tested. Please see dose selection below.

Secondary endpoint results

For the initial treatment period the secondary endpoints results support the effects seen in the Primary Endpoints. For secondary endpoints including those under multiplicity adjustment (i.e. a reduction of Adolescent Worst Pruritus NRS of ≥4 from baseline, change SCORAD and CDLQI from baseline to Week 16, for both doses) statistically significantly better results were reported in patients receiving tralokinumab as compared to patients on placebo.

The choice of primary estimand for the continuous SCORAD and DLQI endpoints is not agreed as the treatment effect under full adherence to assigned treatment without receipt of rescue is not considered to be of primary clinical relevance. The pre-specified primary estimand sensitivity analysis based on placebo-based multiple imputation is preferred and is considered more suitable for presentation in section 5.1 of the SmPC. This issue was highlighted to the applicant during the original MAA and therefore the efficacy results in the SmPC for adolescents are presented in line with analyses presented for the ECZTRA 1, 2 & 3 trials in the adult population.

For change in SCORAD, and reduction of Pruritus NRS ≥4 at Week 16, the placebo response was lower in ECZTRA 6 than in the adult monotherapy pool, and thus the treatment difference to placebo was higher in adolescents than in adults. The results from the CDLQI and DLQI questionnaires cannot be directly compared due to differences in the items to be scored, and therefore no conclusion could be made for this endpoint.

Dose selection summary

In the ECZTRA 6 study in the initial treatment period two doses were tested whereas in the maintenance treatment period four doses were tested i.e 300 mg Q2W, 300 mg Q4W, 150 mg Q2W and 150 mg Q4W. Further, in the open label treatment period patients were receiving tralokinumab 300 mg Q2W with optional use of TCS and/or TCI.

In relation to the efficacy results in the initial treatment period, no significant differences between doses were noted. For IGA 0/1 at Week 16, the differences as compared to placebo was 17.5 (8.4, 26.6) for 150 mg W2Q and 13.8 (5.3, 22.3) for 300 mg W2Q. For EASI75 at Week 16 the differences as compared to placebo was 22.5 (12.4, 32.6) for 150 mg W2Q and 22.0 (12.0,32.0) for 300 mg W2Q.

In relation efficacy beyond week 16 the available data for each particular dose regimen is limited although the highest amount of data are available for 300 mg W2Q + optional TCS regimen as this regimen was tested in 214 subjects transferred to the open label treatment period at week 16. For other monotherapy regimens (i.e 300 mg Q2W, 300 mg Q4W, 150 mg Q2W and 150 mg Q4W) investigated in the maintenance treatment period no firm conclusion can be made as the number of patients in each treatment group was too small.

In relation to the safety results in the initial treatment period, no major differences between doses were noted although slightly better results were reported unexpectedly for the higher dose (300 mg Q2W). AEs were reported in 67.3% of subjects in the 150 mg Q2W group and 64.9% of subjects in the 300 mg Q2W group. SAEs were reported in 3.1% and 1% of subjects in 150 mg Q2W and 300 mg Q2W groups, respectively. Severe AEs were reported in 5.1% in the 150 mg Q2W group and 3.1% of subjects in the 300 mg Q2W group. For the maintenance treatment period the number of subjects was too small to allow for firm conclusion.

In summary, for the initial treatment period no major differences between doses were noted although for safety slightly better results were reported for the 300 mg Q2W dose.

The applicant was requested to justify the dose proposed for adolescents.

The dose 300 mg Q2W is justified based on the following:

-The tralokinumab 150 mg Q2W and 300 mg Q2W dosing regimens tested in ECZTRA 6 showed similar efficacy on the primary and key secondary endpoints however numerically higher responses in the 300 mg Q2W dosing group were recorded for other clinical relevant endpoints such as responder rates for EASI50, reductions in POEM $\geqslant$6, CDLQI $\geqslant$6 and the reduction in the HADS total score.

-AE of 'dermatitis atopic' (suggesting lack of response) had later onset and the number of such events was lower for tralokinumab 300 mg Q2W as compared to the 150 mg Q2W group

-rescue medications (mainly TCS) were initiated later for tralokinumab 300 mg Q2W as compared to the 150 mg Q2W group

-absence of exposure-related safety concerns (as in the 300 mg Q2W group less TEAEs were reported as compared to the 150 mg Q2W group).

Therefore, the CHMP endorsed the 300 mg Q2W dose.

Efficacy beyond Week 16

A long-term efficacy was assessed in the maintenance period and in open-label treatment period.

The maintenance period included subjects who achieved clinical response at Week 16 without use of rescue medication from Week 2 to Week 16. During this period, four doses were tested i.e 300 mg Q2W, 300 mg Q4W, 150 mg Q2W, 150 mg Q4W. Non-responders at Week 16 and subjects who lost their response were transferred to the open-label treatment period where they were receiving tralokinumab 300 mg Q2W with optional use of TCS and/or TCI.

In relation to the efficacy results beyond Week 16, they are comparable between adults and adolescents however the strength of evidence is lower as compared to the initial treatment period.

Although percentage of responders in the maintenance period in ECZTRA 6 was similar to percentage of responders in the monotherapy pool (ECZTRA 1+2) these results should be interpreted with caution due to the low number of subjects in each treatment group (ranging from 11-14 subjects in the tralokinumab groups) in ECZTRA 6. Further, endpoints in the maintenance period were not included in the multiplicity control strategy.

The posology for adolescents is proposed to be the same as for adults i.e there is an option for every fourth week dosing after 16 weeks of treatment. However, 13 subjects were included in the maintenance period in the 300 mg Q4W arm.

It is noted, that in the open-label treatment period the percentage of responders increased overtime. Among the 214 subjects who transferred to open-label treatment at Week 16, 31.3% (95% CI: 25.5 to 37.8) achieved IGA 0/1 at Week 52 and 60.7% (95% CI: 54.1 to 67.0) achieved EASI75 at Week 52. However, the results in the open-label treatment were confounded by the fact that 50 % of subjects receiving TCSs in this period.

The applicant acknowledged that the long term efficacy data in adolescents are limited however given that the efficacy and safety profile of tralokinumab 300 mg is overall consistent for the adolescent and adult trial populations, extrapolation of maintenance data from adults to adolescents is warranted. This justification was accepted by CHMP. It was also noted that the long-term study ECZTEND is ongoing and the applicant will provide the CTR in Q4 2022.

Subgroups

To assess the consistency in response rates for the primary endpoints across different subgroups, the primary endpoints (IGA 0/1 and EASI75) in ECZTRA 6 were summarised by the following subgroups:

- Baseline IGA (moderate, severe).
- Region (North America, Europe, Australia, Asia).
- Race (white, Black or African American, Asian, other).
- Sex.
- Age group (12–14 years and 15–17 years).
- Body weight group (≤60 kg and >60 kg).
- Body weight groups (≤55 kg and >55 kg, ≤60 kg and >60 kg, ≤65 kg and >65 kg, ≤70 kg and >70 kg, ≤80 kg and >80 kg).

Better response was observed in patients with moderate disease at baseline as compared to those with severe disease. In the groups of patients with severe disease at baseline there was only less than 10 % IGA 0/1 responders at Week 16 and less than 22 % of EASI75 responders at Week 16. The applicant was requested to discuss the use of the product in adolescents with severe disease.

In adolescents with severe disease the treatment response was lower as compared to adolescents with moderate disease (IGA 3) however the response which was achieved in adolescents with severe disease was similar to the response observed in adult patients with the same level of disease severity investigated in the pivotal studies supporting the original MAA.

In addition, the response which was achieved in adolescents with severe disease could be considered as clinically relevant. A 1-point reduction on the IGA scale represents a clinically meaningful reduction in disease severity, but a subject with IGA=4 at baseline needed at least a 3-point reduction in IGA to achieve IGA 0/1. Based on the baseline EASI score in subjects with IGA=4 at baseline (mean = 40.4; minimum = 16). a 75% reduction in EASI score in this subgroup was much larger than the 6.6-point reduction identified as the MCID on the EASI scale. The CHMP considered the applicant's explanation acceptable.

Analyses of interaction between treatment and subgroups for IGA 0/1 or EASI75 response rates suggested treatment response variation among age subgroups for IGA 0/1 at Week 16 (p=0.02) and among body weight subgroups (≤60 kg versus >60 kg) for EASI75 at Week 16 (p=0.03). In the tralokinumab 150 mg Q2W group, the response rates were higher in the younger subjects. In relation to body weight (≤60 kg vs. >60 kg). For both IGA 0/1 and EASI75, response rates were higher in subjects with a body weight ≤60 kg in the tralokinumab 300 mg Q2W group and higher in subjects with a body weight >60 kg in the tralokinumab 150 mg Q2W group. The applicant was requested to provide a potential explanation of these results. The applicant discussed the observed variation in IGA 0/1 response rate across age groups as well as the observed variation in EASI75 response rate across body weight subgroups and it was agreed that the observed differences are likely to be a chance finding.

2.4.4. Conclusions on the clinical efficacy

The CHMP considered all issues on the clinical efficacy resolved.

2.5. Clinical safety

Introduction

Tralokinumab 150 mg solution for injection was approved by the European Commission on 17-Jun-2021 under the name of Adtralza for the treatment of moderate-to-severe AD in adult patients who are candidates for systemic therapy.

The recommended dosage of tralokinumab in adults is an initial dose of 600 mg followed by 300 mg administered every 2 weeks by SC injection. Tralokinumab can be used with or without TCS.

The purpose of this submission is to provide data supporting the use of tralokinumab in adolescents (12–17 years) with AD.

The data supporting the use of tralokinumab in adolescents derive from 1 pivotal trial and 2 supportive trials:

Pivotal trial:

- ECZTRA 6 – a completed phase 3 trial in adolescent subjects with moderate-to-severe AD who received tralokinumab (150 mg or 300 mg) or placebo for up to 52 weeks. This study is the primary source of new safety data included in this application.

Supportive trials:

- ECZTEND – an ongoing phase 3 extension trial in subjects with moderate-to-severe AD, including adolescent subjects who completed ECZTRA 6 and who will receive tralokinumab 300 mg Q2W open-label in ECZTEND. As this trial is ongoing, only information on exposure, SAEs, and AEs leading to permanent discontinuation of IMP for the adolescent subjects transferred from ECZTRA 6 is included in this application as additional long-term safety data. The data cut-off for the safety data from ECZTEND is 31-Mar-2021.
- CD-RI-CAT-354-1054 – a completed phase 1 trial in adolescent subjects with asthma who received a single dose of tralokinumab 300 mg.

Patient exposure

The overall extent of exposure to IMP in the 3 clinical trials which enrolled adolescents is presented below:

Panel 52 ***Total exposure in trials with tralokinumab in adolescent subjects***

Trial	Tralokinumab, SC						Placebo, SC	
	150 mg		300 mg		All			
	N	Total PYE	N	Total PYE	N	Total (mean) PYE	N	Total (mean) PYE
ECZTRA 6	[a]	42.3	[a]	193.0	276	235.3 (0.852)	94	30.9 (0.329)
ECZTEND[b]	-	-	127	84.0	127	84.0	-	-
CD-RI-CAT-354-1054	-	-	20	Single dose	20	Single dose	-	-

Notes: a = A subject could have contributed with exposure time in a 150 mg treatment arm (dosed either Q2W or Q4W) as well as in the 300 mg Q2W open-label arm. The 300 mg column includes all subjects dosed with tralokinumab 300 mg (Q2W or Q4W), including open-label Q2W. Hence, only the total number of subjects exposed to tralokinumab is included (in the 'All' column); **b** = Data cut-off: 31-Mar-2021.

Abbreviations: N = number of subjects; PYE = patient years of exposure; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous.

In ECZTRA 6, the total exposure to tralokinumab was 235 PYE (mean: 0.852 PYE), and the total exposure to placebo was 31 PYE (mean: 0.329 PYE).

In ECZTRA 6, 166 (60.1%) of the subjects were exposed to tralokinumab for 52 weeks or more; the corresponding number for placebo was 4 (4.3%) subjects. A majority of the remaining subjects were exposed to tralokinumab for at least 36 weeks, reflecting that most subjects who received placebo during the initial 16 weeks were subsequently transferred to open-label treatment with tralokinumab 300 mg Q2W.

Panel 53 ***ECZTRA 6 Exposure time, entire treatment period: safety analysis set***

	Tralokinumab 150 mg Q2W (n=98)	Tralokinumab 150 mg Q4W (n=14)	Tralokinumab 300 mg Q2W (n=97)	Tralokinumab 300 mg Q4W (n=13)	Tralokinumab 300 mg Q2W + optional TCS (n=234)	Tralokinumab total (n=276)	Placebo (n=94)
PYE (Years)							
N	98	14	97	13	234	276	94
SUM	35.74	6.53	35.09	6.78	151.12	235.25	30.91
Mean (SD)	0.365 (0.205)	0.466 (0.282)	0.362 (0.181)	0.522 (0.244)	0.646 (0.128)	0.852 (0.223)	0.329 (0.154)
Median	0.307	0.687	0.307	0.686	0.691	0.995	0.307
Q1;Q3	(0.306;0.315)	(0.260;0.691)	(0.304;0.315)	(0.376;0.691)	(0.680;0.694)	(0.691;0.998)	(0.304;0.310)
Min;max	0.03;1.01	0.04;0.71	0.09;1.03	0.07;0.71	0.04;0.77	0.03;1.07	0.00;1.02
Exposure time, N (%)							
N (%)	98 (100.0)	14 (100.0)	97 (100.0)	13 (100.0)	234 (100.0)	276 (100.0)	94 (100.0)
< 6 weeks	3 (3.1)	3 (21.4)	1 (1.0)	1 (7.7)	2 (0.9)	4 (1.4)	3 (3.2)
6 - 11 weeks	2 (2.0)		1 (1.0)	1 (7.7)	4 (1.7)	5 (1.8)	1 (1.1)
12 - 17 weeks	77 (78.6)	3 (21.4)	82 (84.5)	1 (7.7)	8 (3.4)	3 (1.1)	81 (86.2)
18 - 23 weeks	6 (6.1)		3 (3.1)	1 (7.7)	4 (1.7)	3 (1.1)	4 (4.3)
24 - 29 weeks			1 (1.0)	1 (7.7)	8 (3.4)	9 (3.3)	1 (1.1)
30 - 35 weeks	1 (1.0)				34 (14.5)	13 (4.7)	
36 - 41 weeks	1 (1.0)	8 (57.1)	3 (3.1)	8 (61.5)	174 (74.4)	64 (23.2)	
42 - 47 weeks						1 (0.4)	
48 - 51 weeks			2 (2.1)			8 (2.9)	
>= 52 weeks	8 (8.2)		4 (4.1)			166 (60.1)	4 (4.3)

Adverse events

ECZTRA 6 study

Initial treatment period (Week 0 to Week 16)

In the initial treatment period, the overall proportion of subjects reporting AEs was similar in all treatment groups, although the rate of AEs was higher with tralokinumab 150 mg Q2W than with tralokinumab 300 mg Q2W and placebo:

- 64.9% and 441.0 events per 100 PYE with tralokinumab 300 mg Q2W.
- 67.3% and 596.6 events per 100 PYE with tralokinumab 150 mg Q2W.
- 61.7% and 479.7 events per 100 PYE with placebo.

The majority of AEs in all treatment groups were mild or moderate in severity and the subjects recovered from most of the AEs. There were no clinically relevant differences in distribution across severities between the treatment groups.

9 SAEs were reported in the initial treatment period and all subjects had recovered from the events by the end of the trial, although 1 with sequelae

- 1 event in 1 subject (1.0%, 3.39 events per 100 PYE) with tralokinumab 300 mg Q2W.
- 3 events in 3 subjects (3.1%, 10.23 events per 100 PYE) with tralokinumab 150 mg Q2W.
- 5 events in 5 subjects (5.3%, 17.90 events per 100 PYE) with placebo.

The proportion of subjects with AEs assessed as possibly or probably related to IMP by the investigator (hereafter termed as 'related' AEs) was similar in all treatment groups, while the rate was higher with tralokinumab 150 mg Q2W compared with tralokinumab 300 mg Q2W and placebo.

Only 1 AE led to permanent discontinuation of IMP ('drug withdrawn'; reported in the tralokinumab 150 mg Q2W group).

Panel 54 ***Overall summary of adverse events, initial treatment period: safety analysis set***

	Tralokinumab 150 mg Q2W (n=98, PYE=29.33)				Tralokinumab 300 mg Q2W (n=97, PYE=29.48)				Placebo (n=94, PYE=27.93)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Events	66	(67.3)	175	596.6	63	(64.9)	130	441.0	58	(61.7)	134	479.7
Serious	3	(3.1)	3	10.23	1	(1.0)	1	3.39	5	(5.3)	5	17.90
Severity												
Mild	48	(49.0)	109	371.6	47	(48.5)	81	274.8	40	(42.6)	77	275.7
Moderate	33	(33.7)	56	190.9	32	(33.0)	45	152.6	31	(33.0)	50	179.0
Severe	5	(5.1)	10	34.09	3	(3.1)	4	13.57	7	(7.4)	7	25.06
Related to IMP *	26	(26.5)	54	184.1	25	(25.8)	39	132.3	20	(21.3)	36	128.9
Leading to withdrawal	1	(1.0)	1	3.41	0				0			
Outcome												
Fatal	0				0				0			
Not recovered/Not resolved	6	(6.1)	8	27.27	5	(5.2)	5	16.96	7	(7.4)	7	25.06
Recovering/Resolving	4	(4.1)	5	17.05	1	(1.0)	1	3.39	2	(2.1)	2	7.16
Recovered/Resolved	63	(64.3)	161	548.9	59	(60.8)	122	413.8	55	(58.5)	121	433.2
Recovered/Resolved with sequelae	1	(1.0)	1	3.41	0				3	(3.2)	3	10.74
Unknown	0				2	(2.1)	2	6.78	1	(1.1)	1	3.58
Action taken with IMP												
Dose not changed	64	(65.3)	161	548.9	58	(59.8)	120	407.0	56	(59.6)	122	436.8
Dose reduced	0				0				0			
Dose increased	0				0				0			
Drug interrupted	3	(3.1)	3	10.23	3	(3.1)	3	10.18	3	(3.2)	3	10.74
Drug withdrawn	1	(1.0)	1	3.41	0				0			
Not applicable	4	(4.1)	10	34.09	6	(6.2)	7	23.74	5	(5.3)	9	32.22
Unknown	0				0				0			

AEs collected during the exposure time in the initial treatment period are shown.

Maintenance treatment period (Week 16 to Week 52)

The safety data for the **maintenance treatment period** should be interpreted with caution due to the low number of subjects in each treatment group.

AEs were overall reported at a lower rate for tralokinumab Q2W in the maintenance treatment period compared with tralokinumab Q2W in the initial treatment period for both doses.

- Tralokinumab 300 mg Q2W:
  - 441.0 events per 100 PYE in the initial treatment period.
  - 231.8 events per 100 PYE in the maintenance treatment period.
- Tralokinumab 150 mg Q2W:
  - 596.6 events per 100 PYE in the initial treatment period.
  - 343.6 events per 100 PYE in the maintenance treatment period.

In the maintenance treatment period, the rate of AEs varied across treatment groups without any pattern being observed (rates ranging from 103.2 events per 100 PYE to 343.6 events per 100 PYE between all treatment groups).

Except for 1 severe AE reported in the tralokinumab 300 mg Q2W/Q2W group, all AEs were mild or moderate in severity. The subjects recovered from most of the AEs. No SAEs were reported in the maintenance treatment period.

The rate of related AEs varied across treatment groups with no pattern being observed.

No AEs led to permanent discontinuation of IMP.

Panel 55 ***Overall summary of adverse events, maintenance treatment period: safety analysis set***

	Week 16 Tralokinumab 150 mg Q2W responders								Week 16 Tralokinumab 300 mg Q2W responders								Week 16 Placebo responders			
	Tralokinumab 150 mg Q2W (n=12, PYE=6.4)				Tralokinumab 150 mg Q4W (n=14, PYE=6.53)				Tralokinumab 300 mg Q2W (n=11, PYE=5.61)				Tralokinumab 300 mg Q4W (n=13, PYE=6.78)				Placebo (n=6, PYE=2.98)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Events	7	(58.3)	22	343.6	8	(57.1)	10	153.2	7	(63.6)	13	231.8	6	(46.2)	7	103.2	4	(66.7)	4	134.2
Serious	0				0				0				0				0			
Severity																				
Mild	4	(33.3)	9	140.6	5	(35.7)	5	76.62	4	(36.4)	5	89.15	3	(23.1)	4	58.96	1	(16.7)	1	33.55
Moderate	6	(50.0)	13	203.0	4	(28.6)	5	76.62	6	(54.5)	7	124.8	3	(23.1)	3	44.22	3	(50.0)	3	100.6
Severe	0				0				1	(9.1)	1	17.83	0				0			
Related to IMP *	3	(25.0)	9	140.6	3	(21.4)	5	76.62	2	(18.2)	3	53.49	2	(15.4)	2	29.48	1	(16.7)	1	33.55
Leading to withdrawal	0				0				0				0				0			
Outcome																				
Fatal	0				0				0				0				0			
Not recovered/Not resolved	0				2	(14.3)	2	30.65	2	(18.2)	3	53.49	1	(7.7)	1	14.74	0			
Recovering/Resolving	1	(8.3)	1	15.62	1	(7.1)	1	15.32	0				0				0			
Recovered/Resolved	7	(58.3)	21	328.0	5	(35.7)	7	107.3	7	(63.6)	10	178.3	5	(38.5)	6	88.43	4	(66.7)	4	134.2
Recovered/Resolved with sequelae	0				0				0				0				0			
Unknown	0				0				0				0				0			
Action taken with IMP																				
Dose not changed	7	(58.3)	21	328.0	7	(50.0)	9	137.9	7	(63.6)	12	214.0	5	(38.5)	6	88.43	4	(66.7)	4	134.2
Dose reduced	0				0				0				0				0			
Dose increased	0				0				0				0				0			
Drug interrupted	0				0				0				0				0			
Drug withdrawn	0				0				0				0				0			
Not applicable	1	(8.3)	1	15.62	1	(7.1)	1	15.32	1	(9.1)	1	17.83	1	(7.7)	1	14.74	0			
Unknown	0				0				0				0				0			

AEs collected during the exposure time in the maintenance treatment period are shown.
AE: Adverse event. Q2W: Every 2 weeks. Q4W: Every 4 weeks. PYE: Patient years of exposure. n: Number of subjects in analysis set. N: Number of subjects with one or more events. %: Percentage of subjects with one or more events. E: Number of adverse events. R: Rate (number of events divided by patient years of exposure multiplied by 100). IMP: Investigational medicinal product.
*) Considered possibly or probably related to trial product by the investigator.

Open-label treatment period (Week 16 to Week 52)

The rate of AEs for subjects treated with open-label treatment was 349.4 events per 100 PYE and hence lower than the rate of AEs with tralokinumab Q2W in the initial treatment period (441.0 events per 100 PYE with tralokinumab 300 mg Q2W and 596.6 events per 100 PYE with tralokinumab 150 mg Q2W).

The majority of AEs reported for subjects treated with open-label treatment were mild or moderate in severity and the subjects recovered from most of the AEs. Severe AEs were reported at a lower rate in subjects who received open-label treatment (2.65 events per 100 PYE) compared with subjects treated with tralokinumab Q2W in the initial treatment period (13.57 events per 100 PYE with tralokinumab 300 mg Q2W and 34.09 events per 100 PYE with tralokinumab 150 mg Q2W).

7 SAEs were reported in 7 subjects at a rate of 4.63 events per 100 PYE in subjects receiving open-label treatment and the rate was comparable with the rate of SAEs with tralokinumab 300 mg Q2W in the initial treatment period (3.39 events per 100 PYE) and lower than the rate of SAEs with tralokinumab 150 mg Q2W in the initial treatment period (10.23 events per 100 PYE).

Related AEs were reported at a lower rate for subjects who received open-label treatment (107.2 events per 100 PYE) compared with subjects treated with tralokinumab Q2W in the initial treatment period (132.3 events per 100 PYE with tralokinumab 300 mg Q2W and 184.1 events per 100 PYE with tralokinumab 150 mg Q2W).

There were 2 AEs that led to permanent discontinuation of IMP at a rate of 1.32 events per 100 PYE and the rate was comparable with the rate of AEs that led to permanent discontinuation of IMP with tralokinumab Q2W in the initial treatment period (0 events per 100 PYE with tralokinumab 300 mg Q2W and 3.41 events per 100 PYE with tralokinumab 150 mg Q2W).

Panel 56 ***Overall summary of adverse events, open-label treatment: open-label safety analysis set***

	Tralokinumab 300 mg Q2W + optional TCS (n=234, PYE=151.12)			
	N	(%)	E	R
Events	158	(67.5)	528	349.4
Serious	7	(3.0)	7	4.63
Severity				
Mild	122	(52.1)	361	238.9
Moderate	82	(35.0)	163	107.9
Severe	4	(1.7)	4	2.65
Related to IMP *	65	(27.8)	162	107.2
Leading to withdrawal	2	(0.9)	2	1.32
Outcome				
Fatal	0			
Not recovered/Not resolved	27	(11.5)	38	25.15
Recovering/Resolving	22	(9.4)	27	17.87
Recovered/Resolved	151	(64.5)	461	305.1
Recovered/Resolved with sequelae	1	(0.4)	2	1.32
Unknown	0			
Action taken with IMP				
Dose not changed	151	(64.5)	470	311.0
Dose reduced	1	(0.4)	1	0.66
Dose increased	0			
Drug interrupted	13	(5.6)	16	10.59
Drug withdrawn	2	(0.9)	2	1.32
Not applicable	19	(8.1)	39	25.81
Unknown	0			

AEs collected during the exposure time in the open-label treatment period are shown.
AE: Adverse event. TCS: topical corticosteroid. Q2W: Every 2 weeks. PYE: Patient years of exposure. n: Number of subjects in analysis set. N: Number of subjects with one or more events. %: Percentage of subjects with one or more events. E: Number of adverse events. R: Rate (number of events divided by patient years of exposure multiplied by 100). IMP: Investigational medicinal product.
*) Considered possibly or probably related to trial product by the investigator.

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Entire treatment period (Week 0 to Week 52)

During the entire treatment period, AEs were reported in 214 out of 276 subjects (77.5%) exposed to any dose regimen of tralokinumab ('tralokinumab total') at a rate of 376.2 events per 100 PYE. For placebo, the numbers were 60 out of 94 subjects (63.8%) at a rate of 446.4 events per 100 PYE.

Safety follow-up period (Week 52 to Week 66)

In the safety follow-up period, the overall proportion of subjects reporting AEs and the rate of AEs in subjects who had been treated with tralokinumab 150 mg Q2W, tralokinumab 150 mg Q4W, tralokinumab 300 mg Q2W, and/or tralokinumab 300 mg Q4W ('tralokinumab 150/300 mg Q2W/Q4W') were generally low and comparable with those in subjects who had received open-label treatment ('tralokinumab 300 Q2W + TCS') and placebo.

- 14.7% and 98.49 events per 100 PYE after treatment with tralokinumab 150/300 mg
  - Q2W/Q4W.
- 14.4% and 94.08 events per 100 PYE after open-label treatment.

- 16.7% and 84.16 events per 100 PYE after receiving placebo.

The majority of AEs were mild or moderate in severity and the subjects recovered from most of the AEs. 5 severe AEs were reported: 1 after treatment with tralokinumab 150/300 mg Q2W/Q4W (2.9%, 14.07 events per 100 PYE) and 4 after open-label treatment (2.1%, 8.75 events per 100 PYE).

3 SAEs were reported in the safety follow-up period, all in subjects who had received open-label treatment (1.5%, 6.56 events per 100 PYE).

AEs assessed as related to IMP were only reported in subjects who had received open-label treatment (1.5%, 6.56 events per 100 PYE).

No AEs led to withdrawal from the trial.

Panel 57 ***Overall summary of adverse events, safety follow-up period: safety follow-up analysis set***

	Tralokinumab 150/300 mg Q2W/Q4W (n=34, PYFU=7.11)				Tralokinumab 300 mg Q2W + TCS (n=194, PYFU=45.71)				Placebo (n=6, PYFU=1.19)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Events	5	(14.7)	7	98.49	28	(14.4)	43	94.08	1	(16.7)	1	84.16
Serious	0				3	(1.5)	3	6.56	0			
Severity												
Mild	2	(5.9)	2	28.14	18	(9.3)	25	54.70	1	(16.7)	1	84.16
Moderate	4	(11.8)	4	56.28	11	(5.7)	14	30.63	0			
Severe	1	(2.9)	1	14.07	4	(2.1)	4	8.75	0			
Related to IMP *	0				3	(1.5)	3	6.56	0			
Leading to withdrawal	0				0				0			
Outcome												
Fatal	0				0				0			
Not recovered/Not resolved	1	(2.9)	1	14.07	10	(5.2)	10	21.88	0			
Recovering/Resolving	1	(2.9)	1	14.07	6	(3.1)	7	15.32	1	(16.7)	1	84.16
Recovered/Resolved	4	(11.8)	4	56.28	17	(8.8)	25	54.70	0			
Recovered/Resolved with sequelae	0				0				0			
Unknown	1	(2.9)	1	14.07	1	(0.5)	1	2.19	0			
Action taken with IMP												
Dose not changed	1	(2.9)	1	14.07	2	(1.0)	4	8.75	0			
Dose reduced	0				0				0			
Dose increased	0				0				0			
Drug interrupted	0				0				0			
Drug withdrawn	0				0				0			
Not applicable	5	(14.7)	6	84.42	27	(13.9)	39	85.33	1	(16.7)	1	84.16
Unknown	0				0				0			

Comparisons to adults

Panel 58 ***Overall summary of AEs - initial treatment period - AD pool vs ECZTRA 6 - adjusted pooling - safety analysis set***

	AD pool				ECZTRA 6											
	Tralokinumab 300 mg Q2W (n=1605, PYE=473.21)				Tralokinumab 150 mg Q2W (n=98, PYE=29.33)				Tralokinumab 300 mg Q2W (n=97, PYE=29.48)				Tralokinumab Total (n=195, PYE=58.81)			
	N	(adj.%)	E	adj.R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Events	1082	(65.9)	3153	640.7	66	(67.3)	175	596.6	63	(64.9)	130	441.0	129	(66.2)	305	518.6
Serious	37	(2.1)	38	7.4	3	(3.1)	3	10.2	1	(1.0)	1	3.4	4	(2.1)	4	6.8
Severity																
Mild	883	(53.3)	2132	431.0	48	(49.0)	109	371.6	47	(48.5)	81	274.8	95	(48.7)	190	323.0
Moderate	518	(31.5)	917	189.5	33	(33.7)	56	190.9	32	(33.0)	45	152.6	65	(33.3)	101	171.7
Severe	77	(4.6)	104	20.2	5	(5.1)	10	34.1	3	(3.1)	4	13.6	8	(4.1)	14	23.8
Related to IMP *	464	(28.0)	1026	207.9	26	(26.5)	54	184.1	25	(25.8)	39	132.3	51	(26.2)	93	158.1
Leading to withdrawal from trial	35	(2.1)	43	9.0	1	(1.0)	1	3.4	0				1	(0.5)	1	1.7

	AD pool				ECZTRA 6			
	Placebo (n=680, PYE=193.1)				Placebo (n=94, PYE=27.93)			
	N	(adj.%)	E	adj.R	N	(%)	E	R
Events	450	(67.4)	1278	679.2	58	(61.7)	134	479.7
Serious	18	(2.8)	22	11.9	5	(5.3)	5	17.9
Severity								
Mild	328	(49.3)	740	391.9	40	(42.6)	77	275.7
Moderate	258	(39.0)	478	254.3	31	(33.0)	50	179.0
Severe	40	(6.3)	60	33.0	7	(7.4)	7	25.1
Related to IMP *	176	(26.8)	365	195.6	20	(21.3)	36	128.9
Leading to withdrawal from trial	13	(2.0)	16	8.6	0			

AEs collected during the exposure time in the initial treatment period are shown. AE: Adverse event. Q2W: Every 2 weeks. IMP: Investigational medicinal product. PYE: Patient years of exposure. n: Number of subjects. N: Number of subjects with one or more events. %: Percentage of subjects with one or more events. E: Number of adverse events. R: Rate (number of events divided by patient years of exposure multiplied by 100). adj. %: Adjusted percentage calculated using Cochran-Mantel-Haenszel (CMH) weights. adj. R: Adjusted rate calculated using CMH weights. * Related AEs comprise AEs considered possibly related or probably related by the investigator.

Source: Modified from M2.7.4 Addendum Appendix 1 Tables 2.1.1 and 2.1.2

Adverse events by frequency

In all treatment groups in the initial treatment period, the SOC with the highest incidence and rate of AEs were 'infections and infestations', 'skin and subcutaneous tissue disorders', and 'general disorders and administration site conditions' and the most frequently reported preferred terms were 'viral upper respiratory tract infection', 'dermatitis atopic', and 'upper respiratory tract infection'.

In the maintenance treatment period and in subjects receiving open-label treatment, AEs were generally reported with the same pattern of SOCs and preferred terms as for subjects treated with tralokinumab Q2W in the initial treatment period, with similar or lower rates compared to the initial treatment period.

Initial treatment period (Week 0 to Week 16)

In all treatment groups, the SOCs with the highest incidence and rate of AEs included 'infections and infestations', 'skin and subcutaneous tissue disorders', and 'general disorders and administration site conditions'. 'Viral upper respiratory tract infection', 'dermatitis atopic', and 'upper respiratory tract infection' were the most frequently reported AEs in all treatment groups.

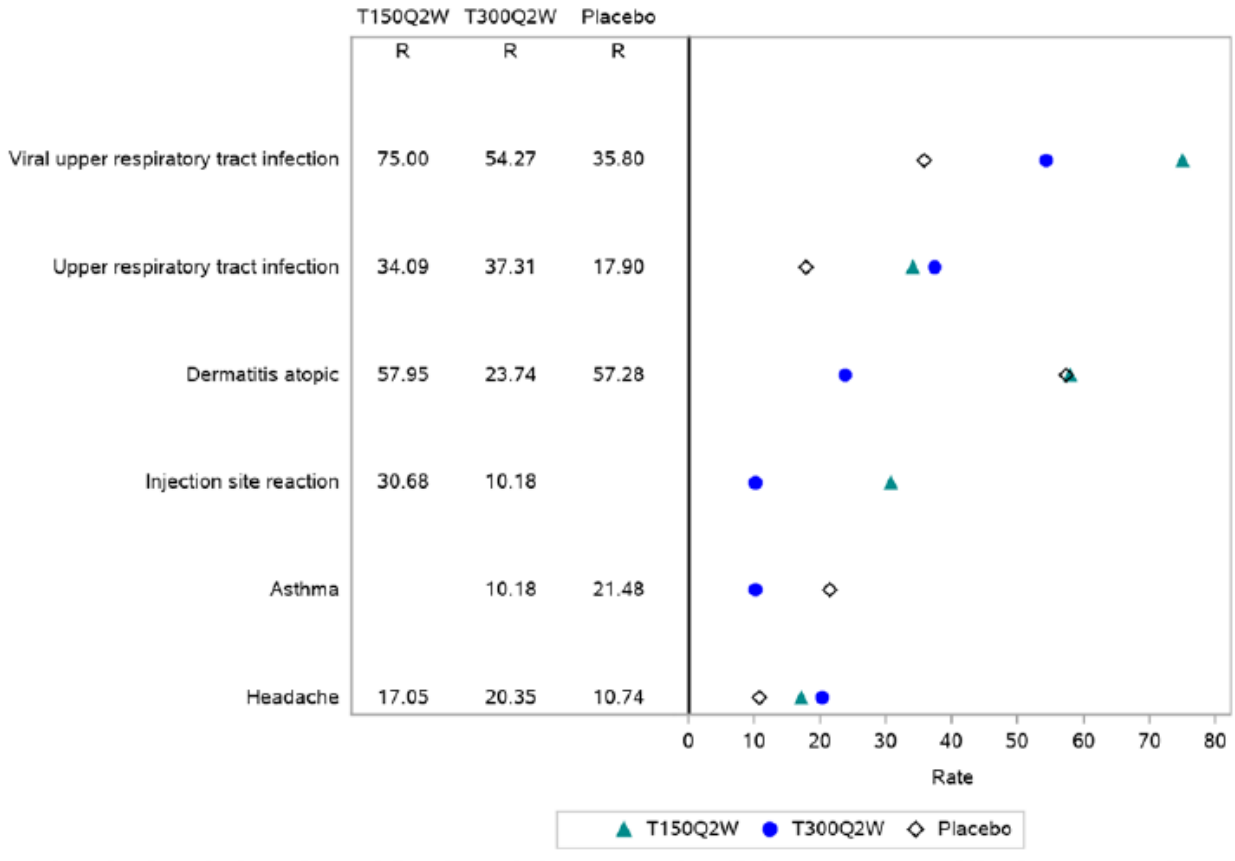
Panel 59 ***Frequent adverse events (≥2% in any treatment group) by system organ class and preferred term, initial treatment period: safety analysis set***

System organ class (SOC) / Preferred term	Tralokinumab 150 mg Q2W (n=98, PYE=29.33)				Tralokinumab 300 mg Q2W (n=97, PYE=29.48)				Placebo (n=94, PYE=27.93)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Infections and infestations												
Viral upper respiratory tract infection	19	(19.4)	22	75.00	12	(12.4)	16	54.27	8	(8.5)	10	35.80
Upper respiratory tract infection	8	(8.2)	10	34.09	11	(11.3)	11	37.31	4	(4.3)	5	17.90
Gastroenteritis	1	(1.0)	1	3.41	3	(3.1)	3	10.18	2	(2.1)	2	7.16
Influenza	2	(2.0)	2	6.82	2	(2.1)	2	6.78	1	(1.1)	1	3.58
Bronchitis	2	(2.0)	2	6.82	2	(2.1)	2	6.78				
Cystitis	2	(2.0)	2	6.82	1	(1.0)	1	3.39				
Skin infection	2	(2.0)	3	10.23	1	(1.0)	2	6.78				
Pharyngitis	2	(2.0)	2	6.82					4	(4.3)	4	14.32
Ear infection	2	(2.0)	2	6.82					2	(2.1)	2	7.16
Tonsillitis					2	(2.1)	2	6.78	1	(1.1)	1	3.58
Conjunctivitis	2	(2.0)	2	6.82								
Gastroenteritis viral					1	(1.0)	1	3.39	2	(2.1)	2	7.16
Staphylococcal skin infection	1	(1.0)	2	6.82					2	(2.1)	2	7.16
Skin and subcutaneous tissue disorders												
Dermatitis atopic	13	(13.3)	17	57.95	7	(7.2)	7	23.74	12	(12.8)	16	57.28
Acne					3	(3.1)	3	10.18	4	(4.3)	4	14.32
Urticaria	2	(2.0)	2	6.82	1	(1.0)	1	3.39	1	(1.1)	1	3.58
General disorders and administration site conditions												
Injection site reaction	6	(6.1)	9	30.68	2	(2.1)	3	10.18				
Injection site pain	3	(3.1)	8	27.27	4	(4.1)	5	16.96	1	(1.1)	1	3.58
Fatigue	4	(4.1)	4	13.64					4	(4.3)	4	14.32
Pyrexia	2	(2.0)	2	6.82					1	(1.1)	2	7.16
Gastrointestinal disorders												
Nausea	3	(3.1)	4	13.64	1	(1.0)	1	3.39				

System organ class (SOC)/ Preferred term	Tralokinumab 150 mg Q2W (n=98, PYE=29.33)				Tralokinumab 300 mg Q2W (n=97, PYE=29.48)				Placebo (n=94, PYE=27.93)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Diarrhoea	2	(2.0)	2	6.82	1	(1.0)	1	3.39	3	(3.2)	3	10.74
Vomiting	2	(2.0)	2	6.82	1	(1.0)	1	3.39	1	(1.1)	1	3.58
Dyspepsia	3	(3.1)	3	10.23								
Abdominal pain upper	1	(1.0)	1	3.41	1	(1.0)	1	3.39	2	(2.1)	2	7.16
Abdominal pain					2	(2.1)	3	10.18				
Constipation					2	(2.1)	2	6.78				
Respiratory, thoracic and mediastinal disorders												
Oropharyngeal pain	1	(1.0)	2	6.82	4	(4.1)	4	13.57	3	(3.2)	3	10.74
Asthma					3	(3.1)	3	10.18	5	(5.3)	6	21.48
Nasal congestion	1	(1.0)	1	3.41	2	(2.1)	2	6.78				
Sinus congestion	2	(2.0)	2	6.82					1	(1.1)	1	3.58
Nervous system disorders												
Headache	5	(5.1)	5	17.05	6	(6.2)	6	20.35	3	(3.2)	3	10.74
Eye disorders												
Conjunctivitis allergic	2	(2.0)	2	6.82	2	(2.1)	2	6.78	2	(2.1)	3	10.74
Eyelid oedema									2	(2.1)	2	7.16
Psychiatric disorders												
Insomnia	3	(3.1)	3	10.23	1	(1.0)	1	3.39	1	(1.1)	1	3.58
Neoplasms benign, malignant and unspecified (incl cysts and polyps)												
Skin papilloma									4	(4.3)	5	17.90

AEs collected during the exposure time in the initial treatment period are shown.
Classification according to MedDRA 20.0. AE: Adverse event. Q2W: Every 2 weeks. n: Number of subjects in analysis set. N: Number of subjects with one or more events. %: Percentage of subjects with one or more events. E: Number of adverse events. R: Rate (number of events divided by patient years of exposure multiplied by 100). PYE: Patient years of exposure. MedDRA: Medical Dictionary for Regulatory Activities.

Panel 60 ***Frequent adverse events (≥5% in any treatment group) by preferred term, initial treatment period: safety analysis set***



A missing rate for a given preferred term and treatment indicates that no such adverse events were observed for that treatment. T150Q2W: Tralokinumab 150 mg every 2 weeks

There were no clinically relevant differences in incidence and rate of AEs in the SOC 'infections and infestations' between the tralokinumab 300 mg Q2W group, the tralokinumab 150 mg Q2W group, and the placebo group.

The most frequently reported preferred term within this SOC was 'viral upper respiratory tract infection', which occurred with higher frequency with tralokinumab 150 mg Q2W compared with tralokinumab 300 mg Q2W and both frequencies were higher than with placebo. The incidence and rate of 'upper respiratory tract infection' were higher with tralokinumab 300 mg Q2W and tralokinumab 150 mg Q2W than with placebo.

- SOC 'infections and infestations':
  - 38.1% and 169.6 events per 100 PYE with tralokinumab 300 mg Q2W.
  - 40.8% and 204.5 events per 100 PYE with tralokinumab 150 mg Q2W.
  - 34.0% and 168.3 events per 100 PYE with placebo.
- Preferred term 'viral upper respiratory tract infection':
  - 12.4% and 54.27 events per 100 PYE with tralokinumab 300 mg Q2W.
  - 19.4% and 75.00 events per 100 PYE with tralokinumab 150 mg Q2W.
  - 8.5% and 35.80 events per 100 PYE with placebo.
- Preferred term 'upper respiratory tract infection':
  - 11.3% and 37.31 events per 100 PYE with tralokinumab 300 mg Q2W.
  - 8.2% and 34.09 events per 100 PYE with tralokinumab 150 mg Q2W.
  - 4.3% and 17.90 events per 100 PYE with placebo.

The incidence and rate of AEs in the SOC 'skin and subcutaneous tissue disorders' were higher with tralokinumab 150 mg Q2W and placebo than with tralokinumab 300 mg Q2W. Within this SOC, 'dermatitis atopic' was the most frequently reported preferred term in all treatment groups and was more common with tralokinumab 150 mg Q2W and placebo than with tralokinumab 300 mg Q2W.

- SOC 'skin and subcutaneous tissue disorders':
  - 12.4% and 44.10 events per 100 PYE with tralokinumab 300 mg Q2W.
  - 21.4% and 85.23 events per 100 PYE with tralokinumab 150 mg Q2W.
  - 18.1% and 85.92 events per 100 PYE with placebo.
- Preferred term 'dermatitis atopic':
  - 7.2% and 23.74 events per 100 PYE with tralokinumab 300 mg Q2W.
  - 13.3% and 57.95 events per 100 PYE with tralokinumab 150 mg Q2W.
  - 12.8% and 57.28 events per 100 PYE with placebo.

The incidence and rate of AEs in the SOC 'general disorders and administration site conditions' were higher with tralokinumab 150 mg Q2W compared with tralokinumab 300 mg Q2W and both were higher than with placebo. This was primarily driven by a higher frequency of events related to injection site reactions in the tralokinumab 300 mg Q2W and tralokinumab 150 mg Q2W groups.

- SOC 'general disorders and administration site conditions':
  - - 10.3% and 44.10 events per 100 PYE with tralokinumab 300 mg Q2W.

- - 15.3% and 98.86 events per 100 PYE with tralokinumab 150 mg Q2W.
- - 5.3% and 25.06 events per 100 PYE with placebo.

Based on the MedDRA search capturing AEs belonging to injection site reactions, the incidence and rate of such AEs were higher with tralokinumab 300 mg Q2W and tralokinumab 150 mg Q2W than with placebo.

The imbalance between tralokinumab Q2W (both 300 mg and 150 mg) and placebo was mainly driven by the preferred terms 'injection site reaction' and 'injection site pain'. All injection site reactions were non-serious and mild or moderate in severity, and the subjects recovered from all the events. All events were assessed as related to IMP and none led to permanent discontinuation of IMP or to withdrawal from trial.

- MedDRA search capturing AEs belonging to injection site reactions:
  - 7.2% and 33.92 events per 100 PYE with tralokinumab 300 mg Q2W.
  - 9.2% and 64.77 events per 100 PYE with tralokinumab 150 mg Q2W.
  - 1.1% and 3.58 events per 100 PYE with placebo.
- Preferred term 'injection site reaction':
  - 2.1% and 10.18 events per 100 PYE with tralokinumab 300 mg Q2W.
  - 6.1% and 30.68 events per 100 PYE with tralokinumab 150 mg Q2W.
  - no events reported with placebo.
- Preferred term 'injection site pain':
  - 4.1% and 16.96 events per 100 PYE with tralokinumab 300 mg Q2W.
  - 3.1% and 27.27 events per 100 PYE with tralokinumab 150 mg Q2W.
  - 1.1% and 3.58 events per 100 PYE with placebo.

The incidence and rate of AEs in the SOC 'eye disorders' were higher with tralokinumab 150 mg Q2W and placebo than with tralokinumab 300 mg Q2W.

- SOC 'eye disorders':
  - 3.1% and 10.18 events per 100 PYE with tralokinumab 300 mg Q2W.
  - 6.1% and 20.45 events per 100 PYE with tralokinumab 150 mg Q2W.
  - 4.3% and 21.48 events per 100 PYE with placebo.

The incidence and rate of AEs in the SOC 'psychiatric disorders' were higher with tralokinumab 150 mg Q2W compared with tralokinumab 300 mg Q2W and both were higher than with placebo. The majority of preferred terms within this SOCs were single events.

- SOC 'psychiatric disorders':
  - 3.1% and 10.18 events per 100 PYE with tralokinumab 300 mg Q2W.
  - 6.1% and 20.45 events per 100 PYE with tralokinumab 150 mg Q2W.
  - 1.1% and 3.58 events per 100 PYE with placebo.

For the remaining SOCs and preferred terms, there was no noteworthy difference between treatment groups in the frequency and distribution pattern of AEs.

Maintenance treatment period (Week 16 to Week 52)

As observed in the initial treatment period, the SOCs with the highest frequency of AEs in the maintenance treatment period included 'infections and infestations' and 'skin and subcutaneous tissue disorders'. The rate of AEs within these SOCs was lower for tralokinumab Q2W in the maintenance treatment period compared with tralokinumab Q2W in the initial treatment period for both doses.

Within the SOC 'infections and infestations', the most frequently reported preferred terms were 'viral upper respiratory tract infection' and 'upper respiratory tract infection'. The most frequently reported preferred term within the SOC 'skin and subcutaneous tissue disorders' was 'dermatitis atopic'.

The remaining SOCs were less common (at most 2 events in either treatment group), except for the SOC 'general disorders and administration site conditions' (6 events of 'malaise' reported in 1 subject in the tralokinumab 150 mg Q2W/Q2W group)

Panel 61 ***Frequent adverse events (≥2% in any tralokinumab Q2W treatment group in the initial treatment period) for tralokinumab Q2W in the initial treatment period vs. the maintenance treatment period by system organ class and preferred term: safety analysis set and maintenance safety analysis set***

	Initial treatment period								Maintenance treatment period							
	Tralokinumab 150 mg Q2W (n=98, PYE=29.33)				Tralokinumab 300 mg Q2W (n=97, PYE=29.48)				Tralokinumab 150 mg Q2W (n=12, PYE=6.4)				Tralokinumab 300 mg Q2W (n=11, PYE=5.61)			
System organ class (SOC) / Preferred term	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Infections and infestations																
Viral upper respiratory tract infection	19	(19.4)	22	75.00	12	(12.4)	16	54.27	1	(8.3)	2	31.24	2	(18.2)	2	35.66
Upper respiratory tract infection	8	(8.2)	10	34.09	11	(11.3)	11	37.31	1	(8.3)	2	31.24	2	(18.2)	2	35.66
Influenza	2	(2.0)	2	6.82	2	(2.1)	2	6.78					2	(18.2)	2	35.66
Pharyngitis	2	(2.0)	2	6.82					3	(25.0)	4	62.48				
Skin and subcutaneous tissue disorders																
Dermatitis atopic	13	(13.3)	17	57.95	7	(7.2)	7	23.74	1	(8.3)	1	15.62				
Acne					3	(3.1)	3	10.18	1	(8.3)	1	15.62				
General disorders and administration site conditions																
Fatigue	4	(4.1)	4	13.64									1	(9.1)	1	17.83
Eye disorders																
Conjunctivitis allergic	2	(2.0)	2	6.82	2	(2.1)	2	6.78	1	(8.3)	1	15.62				

Open-label treatment period (Week 16 to Week 52)

As observed in the initial treatment period, the SOCs with the highest frequency of AEs for subjects receiving open-label treatment were 'infections and infestations' (131.0 events per 100 PYE), 'skin and subcutaneous tissue disorders' (37.06 events per 100 PYE), and 'general disorders and administration site conditions' (45.66 events per 100 PYE).

The most frequent preferred terms for open-label treatment were generally in line with the preferred terms for tralokinumab Q2W in the initial treatment period. The frequent AEs (≥2% in any tralokinumab Q2W treatment group in the initial treatment period) reported for tralokinumab Q2W are presented by SOC and preferred term for the initial treatment period vs. open-label treatment in the panel below.

Panel 62 ***Frequent adverse events (≥2% in any tralokinumab Q2W treatment group in the initial treatment period) for tralokinumab Q2W in the initial treatment period vs. open-label treatment by system organ class and preferred term: safety analysis set and open-label safety analysis set***

	Initial treatment period								Open-label treatment			
	Tralokinumab 150 mg Q2W (n=98, PYE=29.33)				Tralokinumab 300 mg Q2W (n=97, PYE=29.48)				Tralokinumab 300 mg Q2W + optional TCS (n=234, PYE=151.12)			
System organ class (SOC) / Preferred term	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Infections and infestations												
Viral upper respiratory tract infection	19	(19.4)	22	75.00	12	(12.4)	16	54.27	44	(18.8)	60	39.70
Upper respiratory tract infection	8	(8.2)	10	34.09	11	(11.3)	11	37.31	25	(10.7)	34	22.50
Gastroenteritis	1	(1.0)	1	3.41	3	(3.1)	3	10.18	2	(0.9)	3	1.99
Influenza	2	(2.0)	2	6.82	2	(2.1)	2	6.78	3	(1.3)	3	1.99
Bronchitis	2	(2.0)	2	6.82	2	(2.1)	2	6.78	3	(1.3)	3	1.99
Cystitis	2	(2.0)	2	6.82	1	(1.0)	1	3.39	1	(0.4)	2	1.32
Skin infection	2	(2.0)	3	10.23	1	(1.0)	2	6.78	7	(3.0)	9	5.96
Pharyngitis	2	(2.0)	2	6.82					6	(2.6)	6	3.97
Ear infection	2	(2.0)	2	6.82					2	(0.9)	2	1.32
Tonsillitis					2	(2.1)	2	6.78	2	(0.9)	2	1.32
Conjunctivitis	2	(2.0)	2	6.82					4	(1.7)	6	3.97
Skin and subcutaneous tissue disorders												
Dermatitis atopic	13	(13.3)	17	57.95	7	(7.2)	7	23.74	19	(8.1)	26	17.21
Acne					3	(3.1)	3	10.18	3	(1.3)	3	1.99
Urticaria	2	(2.0)	2	6.82	1	(1.0)	1	3.39	4	(1.7)	4	2.65
General disorders and administration site conditions												
Injection site reaction	6	(6.1)	9	30.68	2	(2.1)	3	10.18	10	(4.3)	16	10.59
Injection site pain	3	(3.1)	8	27.27	4	(4.1)	5	16.96	4	(1.7)	20	13.24
Pyrexia	2	(2.0)	2	6.82					5	(2.1)	7	4.63
Gastrointestinal disorders												
Nausea	3	(3.1)	4	13.64	1	(1.0)	1	3.39	6	(2.6)	6	3.97
Diarrhoea	2	(2.0)	2	6.82	1	(1.0)	1	3.39	6	(2.6)	6	3.97
Vomiting	2	(2.0)	2	6.82	1	(1.0)	1	3.39	2	(0.9)	2	1.32
Dyspepsia	3	(3.1)	3	10.23					1	(0.4)	1	0.66
Abdominal pain					2	(2.1)	3	10.18	2	(0.9)	2	1.32
Constipation					2	(2.1)	2	6.78	3	(1.3)	3	1.99
Respiratory, thoracic and mediastinal disorders												
Oropharyngeal pain	1	(1.0)	2	6.82	4	(4.1)	4	13.57	4	(1.7)	4	2.65
Asthma					3	(3.1)	3	10.18	2	(0.9)	3	1.99
Nasal congestion	1	(1.0)	1	3.41	2	(2.1)	2	6.78	1	(0.4)	2	1.32
Nervous system disorders												
Headache	5	(5.1)	5	17.05	6	(6.2)	6	20.35	12	(5.1)	17	11.25
Eye disorders												
Conjunctivitis allergic	2	(2.0)	2	6.82	2	(2.1)	2	6.78	4	(1.7)	4	2.65
Psychiatric disorders												
Insomnia	3	(3.1)	3	10.23	1	(1.0)	1	3.39	2	(0.9)	2	1.32

AEs collected during the exposure time in the initial treatment period and with open-label treatment are shown.
Classification according to MedDRA 20.0. AE: Adverse event. TCS: topical corticosteroid. Q2W: Every 2 weeks. n: Number of subjects in analysis set. N: Number of subjects with one or more events. %: Percentage of subjects with one or more events. E: Number of adverse events. R: Rate (number of events divided by patient years of exposure multiplied by 100). PYE: Patient years of exposure. MedDRA: Medical Dictionary for Regulatory Activities.

As observed in the initial treatment period, 'viral upper respiratory tract infection', 'upper respiratory tract infection', and 'dermatitis atopic' were the most frequent preferred terms.

Based on the MedDRA search capturing AEs belonging to injection site reactions, the rate of such AEs was 26.47 events per 100 PYE and hence slightly lower than the rate observed with tralokinumab Q2W in the initial treatment period (33.92 events per 100 PYE with tralokinumab 300 mg Q2W and 64.77 events per 100 PYE with tralokinumab 150 mg Q2W). The most frequent preferred terms with open-label treatment were 'injection site reaction' (4.3%, 10.59 events per 100 PYE) and 'injection site pain' (1.7%, 13.23 events per 100 PYE). All the injection site reactions were non-serious, all events except for 1 were mild or moderate in severity, and the subjects recovered from all the events. All the events were assessed as related to IMP and none led to permanent discontinuation of IMP or to withdrawal from trial.

Panel 63 ***Frequent adverse events (≥2%) by system organ class and preferred term, open-label treatment: open-label safety analysis set***

System organ class (SOC)/ Preferred term	Tralokinumab 300 mg Q2W + optional TCS (n=234, PYE=151.12) N	(%)	E	R
All AEs	158	(67.5)	528	349.4
Infections and infestations	108	(46.2)	198	131.0
Viral upper respiratory tract infection	44	(18.8)	60	39.70
Upper respiratory tract infection	25	(10.7)	34	22.50
Skin infection	7	(3.0)	9	5.96
Herpes simplex	6	(2.6)	8	5.29
Oral herpes	6	(2.6)	7	4.63
Pharyngitis	6	(2.6)	6	3.97
Skin and subcutaneous tissue disorders	40	(17.1)	56	37.06
Dermatitis atopic	19	(8.1)	26	17.21
Gastrointestinal disorders	28	(12.0)	37	24.48
Diarrhoea	6	(2.6)	6	3.97
Nausea	6	(2.6)	6	3.97
General disorders and administration site conditions	28	(12.0)	69	45.66
Injection site reaction	10	(4.3)	16	10.59
Influenza like illness	5	(2.1)	6	3.97
Pyrexia	5	(2.1)	7	4.63
Respiratory, thoracic and mediastinal disorders	28	(12.0)	40	26.47
Cough	9	(3.8)	10	6.62
Epistaxis	5	(2.1)	9	5.96
Rhinitis allergic	5	(2.1)	5	3.31
Nervous system disorders	20	(8.5)	25	16.54
Headache	12	(5.1)	17	11.25

AEs collected during the exposure time in the open-label treatment period are shown. Classification according to MedDRA 20.0. AE: Adverse event. TCS: topical corticosteroid. Q2W: Every 2 weeks. n: Number of subjects in analysis set. N: Number of subjects with one or more events. %: Percentage of subjects with one or more events. E: Number of adverse events. R: Rate (number of events divided by patient years of exposure multiplied by 100). PYE: Patient years of exposure. MedDRA: Medical Dictionary for Regulatory Activities.

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Safety follow-up period (Week 52 to Week 66)

The incidence and rate of AEs were generally lower in the safety follow-up period compared with the incidence and rate of AEs reported in the treatment periods.

The most frequent preferred terms in the safety follow-up period were 'upper respiratory tract infection' and 'dermatitis atopic'. 'Upper respiratory tract infection' was reported in subjects who had received open-label treatment (1.5%, 6.56 events per 100 PYE). 'Dermatitis atopic' was reported in subjects who had received tralokinumab during maintenance (5.9%, 28.14 events per 100 PYE), in subjects who had received open-label treatment (2.6%, 13.13 events per 100 PYE), and in the placebo group (16.7%, 84.16 events per 100 PYE). All other preferred terms occurred as 1-2 event(s) in 1-2 subject(s) in each treatment group. No pattern in SOCs or preferred terms was observed in this trial period.

No AEs were captured from the MedDRA search on 'injection site reactions.

Comparison to adults

Initial treatment period

The distribution patterns of AEs across SOCs and PTs observed in ECZTRA 6 were generally similar to the patterns observed in the AD pool, except for lower incidences and rates in ECZTRA 6 for AEs reported in the SOC 'skin and subcutaneous tissue disorders' (mainly driven by the PT 'dermatitis atopic') and for the PT 'conjunctivitis'.

Panel 64 ***Main differences in distribution patterns of common AEs reported during the initial treatment period - AD pool vs ECZTRA 6***

System organ class *Preferred term*	AD pool (adults)		ECZTRA 6 (adolescents)		
	Tralokinumab 300 mg Q2W N=1605 Adj% (Adj R)	Placebo N=680 Adj% (Adj R)	Tralokinumab 150 mg Q2W N=98 % (R)	Tralokinumab 300 mg Q2W N=97 % (R)	Placebo N=94 % (R)
Skin and subcutaneous tissue disorders	23.1% (113.7)	34.4% (189.4)	21.4% (85.2)	12.4% (44.1)	18.1% (85.9)
Dermatitis atopic	15.4% (68.0)	26.2% (139.7)	13.3% (58.0)	7.2% (23.7)	12.8% (57.3)
Infections and infestations	38.0% (194.4)	36.5% (200.1)	40.8% (204.5)	38.1% (169.6)	34.0% (168.3)
Conjunctivitis	5.4% (21.0)	1.9% (6.9)	2.0% (6.8)	-	-

With respect to tralokinumab 150 mg versus 300 mg in ECZTRA 6, the data on AEs were generally comparable, except for a lower incidence and rate of the PT 'dermatitis atopic' for tralokinumab 300 mg Q2W.

Open-label treatment period

The distribution patterns of AEs across SOCs and PTs observed during the open-label treatment period in ECZTRA 6 were generally similar to the patterns observed in the monotherapy pool except for a lower incidence and rate in ECZTRA 6 for the PTs 'dermatitis atopic' and 'conjunctivitis'.

Panel 65 ***Main differences in distribution patterns of common AEs reported during open-label treatment - monotherapy pool vs ECZTRA 6***

System organ class *Preferred term*	Monotherapy pool (adults) Tralokinumab 300 mg Q2W N=1121 % (R)	ECZTRA 6 (adolescents) Tralokinumab 300 mg Q2W N=234 % (R)
Skin and subcutaneous tissue disorders	29.4% (87.1)	17.1% (37.1)
Dermatitis atopic	21.2% (56.8)	8.1% (17.2)
Infections and infestations	46.7% (139.1)	46.2% (131.0)
Conjunctivitis	5.6% (11.3)	1.7% (4.0)

Adverse events related to investigational medicinal product

In this trial, both tralokinumab and placebo were IMPs. An AE considered related to IMP was therefore considered related to either tralokinumab or placebo.

AEs considered related to IMP by the investigator are described by trial period below.

Initial treatment period (Week 0 to Week 16)

In the initial treatment period, the proportion of subjects with related AEs was similar in all treatment groups, while the rate was higher with tralokinumab 150 mg Q2W compared with tralokinumab 300 mg Q2W and placebo.

- 25.8% and 132.3 events per 100 PYE with tralokinumab 300 mg Q2W.
- 26.5% and 184.1 events per 100 PYE with tralokinumab 150 mg Q2W.
- 21.3% and 128.9 events per 100 PYE with placebo.

In all treatment groups, the SOCs with the highest frequency of AEs considered related to IMP were 'general disorders and administration site conditions', 'infections and infestations', and 'skin and subcutaneous tissue disorders'.

The incidence and rate of related AEs in the SOC 'general disorders and administration site conditions' were higher with tralokinumab 150 mg Q2W compared with tralokinumab 300 mg Q2W and both were higher than with placebo.

- 7.2% and 33.92 events per 100 PYE with tralokinumab 300 mg Q2W.
- 12.2% and 81.82 events per 100 PYE with tralokinumab 150 mg Q2W.
- 3.2% and 10.74 events per 100 PYE with placebo.

In the tralokinumab groups, the majority of these AEs were related to symptoms at the injection site, e.g. 'injection site reaction' and 'injection site pain', while such events occurred with lower frequencies in the placebo group.

The incidence and rate of related AEs in the SOC 'infections and infestations' were similar in all treatment groups.

- 9.3% and 33.92 events per 100 PYE with tralokinumab 300 mg Q2W.
- 8.2% and 44.32 events per 100 PYE with tralokinumab 150 mg Q2W.
- 8.5% and 46.54 events per 100 PYE with placebo.

Within this SOC, the most common related AE was 'upper respiratory tract infection'

The incidence and rate of related AEs in the SOC 'skin and subcutaneous tissue disorders' were higher with tralokinumab 150 mg Q2W and placebo compared with tralokinumab 300 mg Q2W. The most common related preferred term within this SOC was 'dermatitis atopic', which was more common with placebo compared with tralokinumab 300 mg Q2W and tralokinumab 150 mg Q2W.

- SOC 'skin and subcutaneous tissue disorders':
  - 2.1% and 6.78 events per 100 PYE with tralokinumab 300 mg Q2W.
  - 6.1% and 23.86 events per 100 PYE with tralokinumab 150 mg Q2W.
  - 6.4% and 28.64 events per 100 PYE with placebo.
- Preferred term 'dermatitis atopic':
  - no events reported with tralokinumab 300 mg Q2W.
  - 2.0% and 10.23 events per 100 PYE with tralokinumab 150 mg Q2W.

- 3.2% and 17.90 events per 100 PYE with placebo.

Within the remaining SOCs, no difference between treatment groups in the frequency of related AEs was observed and the majority of AEs occurred as 1-2 event(s) in 1-2 subject(s) in each treatment group.

Panel 66 ***Adverse events related to investigational medicinal product***

System organ class (SOC)/ Preferred term	Tralokinumab 150 mg Q2W (n=98, PYE=29.33)				Tralokinumab 300 mg Q2W (n=97, PYE=29.48)				Placebo (n=94, PYE=27.93)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
All AEs	26	(26.5)	54	184.1	25	(25.8)	39	132.3	20	(21.3)	36	128.9
General disorders and administration site conditions	12	(12.2)	24	81.82	7	(7.2)	10	33.92	3	(3.2)	3	10.74
Injection site reaction	6	(6.1)	9	30.68	2	(2.1)	3	10.18				
Injection site pain	3	(3.1)	8	27.27	4	(4.1)	5	16.96	1	(1.1)	1	3.58
Fatigue	2	(2.0)	2	6.82					2	(2.1)	2	7.16
Injection site oedema	1	(1.0)	1	3.41	1	(1.0)	1	3.39				
Injection site swelling					1	(1.0)	1	3.39				
Injection site urticaria	1	(1.0)	1	3.41								
Malaise	1	(1.0)	2	6.82								
Pyrexia	1	(1.0)	1	3.41								
Infections and infestations	8	(8.2)	13	44.32	9	(9.3)	10	33.92	8	(8.5)	13	46.54
Upper respiratory tract infection	2	(2.0)	3	10.23	3	(3.1)	3	10.18	1	(1.1)	1	3.58
Viral upper respiratory tract infection	2	(2.0)	2	6.82	1	(1.0)	1	3.39	1	(1.1)	1	3.58
Skin infection	1	(1.0)	2	6.82	1	(1.0)	1	3.39				
Body tinea					1	(1.0)	1	3.39				
Bronchitis	1	(1.0)	1	3.41								
Conjunctivitis	1	(1.0)	1	3.41								
Cystitis					1	(1.0)	1	3.39				
Folliculitis	1	(1.0)	1	3.41								
Herpes ophthalmic	1	(1.0)	1	3.41								
Impetigo					1	(1.0)	1	3.39				
Rhinitis					1	(1.0)	1	3.39				
Sinusitis					1	(1.0)	1	3.39				
Staphylococcal skin infection	1	(1.0)	2	6.82								
Atypical pneumonia									1	(1.1)	1	3.58
Ear infection									1	(1.1)	1	3.58
Eczema herpeticum									1	(1.1)	1	3.58
Gastroenteritis									1	(1.1)	1	3.58
Gastroenteritis viral									1	(1.1)	1	3.58
Herpes simplex									1	(1.1)	1	3.58
Oral herpes									1	(1.1)	1	3.58
Otitis media acute									1	(1.1)	1	3.58
Urinary tract infection									1	(1.1)	2	7.16
Viral tonsillitis									1	(1.1)	1	3.58
Skin and subcutaneous tissue disorders	6	(6.1)	7	23.86	2	(2.1)	2	6.78	6	(6.4)	8	28.64
Dermatitis atopic	2	(2.0)	3	10.23					3	(3.2)	5	17.90
Urticaria	1	(1.0)	1	3.41	1	(1.0)	1	3.39				
Alopecia					1	(1.0)	1	3.39				
Diffuse alopecia	1	(1.0)	1	3.41								
Lichen striatus	1	(1.0)	1	3.41								
Petechiae	1	(1.0)	1	3.41								
Acne									1	(1.1)	1	3.58
Pityriasis rosea									1	(1.1)	1	3.58
Skin swelling									1	(1.1)	1	3.58
Gastrointestinal disorders	2	(2.0)	3	10.23	3	(3.1)	3	10.18	1	(1.1)	1	3.58
Nausea	2	(2.0)	3	10.23								
Abdominal pain					1	(1.0)	1	3.39				
Abdominal pain upper					1	(1.0)	1	3.39				
Gastrointestinal pain					1	(1.0)	1	3.39				
Diarrhoea									1	(1.1)	1	3.58
Nervous system disorders	1	(1.0)	1	3.41	3	(3.1)	3	10.18	2	(2.1)	2	7.16
Headache	1	(1.0)	1	3.41	2	(2.1)	2	6.78	1	(1.1)	1	3.58

System organ class (SOC)/ Preferred term	Tralokinumab 150 mg Q2W (n=98, PYE=29.33)				Tralokinumab 300 mg Q2W (n=97, PYE=29.48)				Placebo (n=94, PYE=27.93)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Paraesthesia					1	(1.0)	1	3.39	1	(1.1)	1	3.58
Psychiatric disorders	2	(2.0)	2	6.82	1	(1.0)	1	3.39	1	(1.1)	1	3.58
Insomnia	1	(1.0)	1	3.41	1	(1.0)	1	3.39	1	(1.1)	1	3.58
Panic attack	1	(1.0)	1	3.41								
Respiratory, thoracic and mediastinal disorders	1	(1.0)	1	3.41	2	(2.1)	2	6.78	1	(1.1)	1	3.58
Oropharyngeal pain					2	(2.1)	2	6.78				
Nasal congestion	1	(1.0)	1	3.41								
Asthma									1	(1.1)	1	3.58
Musculoskeletal and connective tissue disorders	1	(1.0)	2	6.82	2	(2.1)	2	6.78				
Myalgia	1	(1.0)	2	6.82	1	(1.0)	1	3.39				
Muscle twitching					1	(1.0)	1	3.39				
Injury, poisoning and procedural complications					2	(2.1)	3	10.18				
Post procedural swelling					1	(1.0)	2	6.78				
Procedural dizziness					1	(1.0)	1	3.39				
Investigations					2	(2.1)	2	6.78				
Blood alkaline phosphatase increased					1	(1.0)	1	3.39				
Blood pressure increased					1	(1.0)	1	3.39				
Eye disorders					1	(1.0)	1	3.39	2	(2.1)	4	14.32
Conjunctivitis allergic					1	(1.0)	1	3.39	1	(1.1)	2	7.16
Dry eye									1	(1.1)	1	3.58
Eyelid oedema									1	(1.1)	1	3.58
Metabolism and nutrition disorders	1	(1.0)	1	3.41								
Hypercalcaemia	1	(1.0)	1	3.41								
Neoplasms benign, malignant and unspecified (incl cysts and polyps)									2	(2.1)	3	10.74
Skin papilloma									2	(2.1)	3	10.74

AEs collected during the exposure time in the initial treatment period are shown.
Classification according to MedDRA 20.0. AE: Adverse event. Q2W: Every 2 weeks. n: Number of subjects in analysis set. N: Number of subjects with one or more events. %: Percentage of subjects with one or more events. E: Number of adverse events. R: Rate (number of events divided by patient years of exposure multiplied by 100). PYE: Patient years of exposure. MedDRA: Medical Dictionary for Regulatory Activities.

Maintenance treatment period (Week 16 to Week 52)

Related AEs were reported at a lower rate for tralokinumab Q2W in the maintenance treatment period compared with tralokinumab Q2W in the initial treatment period.

The rate of related AEs varied across treatment groups with no pattern being observed. Except for tralokinumab 300 mg Q2W/Q4W, all rates were higher than with placebo.

None of these events were serious.

During the maintenance treatment period, all related AEs were reported as at most 1-2 event(s) in 1-2 subject(s) in each treatment group, except for 'malaise' (6 events in 1 of 12 subjects [8.3%] in the tralokinumab 150 mg Q2W/Q2W group). There was no clinically relevant difference between treatment groups in the frequency and distribution pattern of related AEs.

Open-label treatment period (Week 16 to Week 52)

Related AEs were reported at a lower rate in subjects who received open-label treatment (107.2 events per 100 PYE) compared with subjects treated with tralokinumab Q2W in the initial treatment period (132.3 events per 100 PYE for tralokinumab 300 mg Q2W and 184.1 events per 100 PYE for tralokinumab 150 mg Q2W).

As observed in the initial treatment period, the SOCs with the highest frequency of related AEs for subjects receiving open-label treatment were 'infections and infestations', 'general disorders and administration site conditions', and 'skin and subcutaneous tissue disorders'.

The most frequent preferred terms considered related to IMP for open-label treatment were generally the same as those for tralokinumab Q2W in the initial treatment period and most of the events occurred at lower or similar rates with open-label treatment compared tralokinumab Q2W in the initial treatment period.

1 AE assessed as related to IMP ('gastritis') was serious.

Safety follow-up period (Week 52 to Week 66)

In the safety follow-up period, AEs assessed as related to IMP were only reported after open-label treatment (1.5%, 6.56 events per 100 PYE). All 3 related AEs were reported as single events within each SOC. None of these events were serious.

Adverse events by severity

Overall, the vast majority of AEs reported in the trial were mild or moderate in severity. In total, 31 severe AEs were reported, 21 events in the initial treatment period, 1 event in the maintenance treatment period, 4 events in subjects receiving open-label treatment, and 5 events in the safety follow-up period.

In the initial treatment period, 21 severe AEs were reported with no pattern in SOCs or preferred terms. 1 of the 21 severe AEs led to permanent discontinuation of IMP and to withdrawal from the trial.

In the maintenance treatment period, 1 severe AE was reported.

In subjects receiving open-label treatment, 4 severe AEs was reported. 2 AEs of moderate severity led to permanent discontinuation of IMP and also to withdrawal from the trial.

In the safety follow-up period, 5 severe AEs were reported.

Severe adverse events (Week 0 to Week 16)

In all treatment groups, all severe AEs were reported as single events across a number of SOCs and preferred terms, except for 'dermatitis atopic'

- 1 event in 1 subject (1.0%, 3.39 events per 100 PYE) with tralokinumab 300 mg Q2W.
- 3 events in 3 subjects (3.1%, 10.23 events per 100 PYE) with tralokinumab 150 mg Q2W.
- 3 events in 3 subjects (3.2%, 10.74 events per 100 PYE) with placebo).
- 1 severe AE ('cerebrovascular accident' in the tralokinumab 150 Q2W group) led to permanent discontinuation of IMP and also to withdrawal from the trial for 1 subject). This event was reported as serious.

Maintenance treatment period (Week 16 to Week 52)

1 severe AE was reported: the AE 'cataract' reported in a subject in the tralokinumab 300 mg Q2W/Q2W group. The event was non-serious, considered not related to IMP, did not lead to permanent discontinuation of IMP or withdrawal from the trial, and did not resolve by the end of the trial.

Open-label treatment period (Week 16 to Week 52)

In each severity category, most of the individual preferred terms with open-label treatment were generally the same as those in the tralokinumab Q2W groups in the initial treatment period and most of the events occurred at lower or similar rates with open-label treatment compared with tralokinumab Q2W in the initial treatment period.

In total, 4 severe AEs were reported ('injection site pain', 'anaphylactic reaction', 'appendicitis perforated', and 'anorexia nervosa') in 4 subjects receiving open-label treatment. These events were all serious and considered not related to IMP, except for 'injection site pain', which was non-serious and considered probably related to IMP

Safety follow-up period (Week 52 to Week 66)

All 5 severe AEs during the safety follow-up period ('anaphylactic reaction', 'intentional overdose', 'lipoprotein (a) increased', 'renal injury', and 'dermatitis atopic') were reported as single events in single subjects in each treatment group within each SOC. 3 of these events ('anaphylactic reaction', 'intentional overdose', and 'renal injury') were serious and all were considered not related to IMP.

Serious adverse event/deaths/other significant events

Deaths

No deaths were reported during the trial.

Other serious adverse events

Overall, SAEs were reported with low frequencies in all treatment groups in the entire trial and no pattern in SOCs or preferred terms was apparent. In total, 19 SAEs were reported: 9 in the initial treatment period, 7 with open-label treatment, and 3 in the safety follow-up treatment period. All SAEs were moderate or severe, all except for 1 SAE were assessed as not related to IMP by the investigator.

Initial treatment period (Week 0 to Week 16)

9 SAEs were reported in the initial treatment period.

- 1 event in 1 subject (1.0%) with tralokinumab 300 mg Q2W (3.39 events per 100 PYE).
- 3 events in 3 subjects (3.1%) with tralokinumab 150 mg Q2W (10.23 events per 100 PYE).
- 5 events in 5 subjects (5.3%) with placebo (17.90 events per 100 PYE).

Panel 67 ***Overview of serious adverse events, initial treatment period: safety analysis set***

System organ class Preferred term	Severity	Relation to IMP	Outcome	AESI
Tralokinumab 150 mg Q2W				
Infections and infestations				
Cellulitis	Severe	Not related	Recovered/resolved	Yes
Skin and subcutaneous tissue disorders				
Dermatitis atopic	Severe	Not related	Recovered/resolved	No
Nervous system disorders				
Cerebrovascular accident	Severe	Not related	Recovered/resolved with sequelae	No
Tralokinumab 300 mg Q2W				
Injury, poisoning and procedural complications				
Radius fracture	Moderate	Not related	Recovered/resolved	No
Placebo				
Infections and infestations				
Infectious mononucleosis	Moderate	Not related	Recovered/resolved	No
Skin and subcutaneous tissue disorders				
Dermatitis atopic	Severe	Not related	Recovered/resolved	No
Respiratory, thoracic and mediastinal disorders				
Acute respiratory failure	Severe	Not related	Recovered/resolved	No
Asthma	Severe	Not related	Recovered/resolved	No
Immune system disorders				
Anaphylactic reaction	Severe	Not related	Recovered/resolved	No

AESI = adverse event of special interest; IMP = investigational medicinal product; Q2W = every 2 weeks.

Description of SAEs reported in the treatment arms:

1 subject in the tralokinumab 150 mg Q2W group had a severe 'cerebrovascular accident' (reported term: 'stroke') with hospitalisation 57 days after first dose of tralokinumab. The subject was discharged 3 days after the onset of the SAE. The subject was treated with acetylsalicylic acid and ondansetron. The subject's risk factors for stroke included hyperlipidemia, pre-diabetes, and elevated lipoprotein A. The suspected cause for the SAE was elevated lipoprotein A. The event was considered not related to IMP by both the investigator and the sponsor and led to permanent discontinuation of IMP and to withdrawal from trial. The outcome was reported as recovered with sequelae (numbness and tingling in right foot) after 335 days.

1 subject in the tralokinumab 150 mg Q2W group had severe 'cellulitis' 79 days after first and 9 days after latest dose of tralokinumab. The subject was hospitalised 2 days after onset of the SAE and was treated with several treatments including intravenous antibiotics, intravenous antivirals, and pain medications along with several wound care treatments. The subject was discharged 3 days after hospitalisation and the outcome was reported as recovered 13 days after onset of the SAE. The subject's medical history included 3 prior episodes of cellulitis. IMP treatment was continued. The event was considered not related to IMP by both the investigator and the sponsor.

1 subject in the tralokinumab 300 mg Q2W group had a moderate 'radius fracture' after falling from a bicyle 21 days after first and 9 days after latest dose of tralokinumab.

1 subject in the tralokinumab 150 mg Q2W group had severe 'dermatitis atopic' (reported term: 'worsening of atopic dermatitis flare') 94 days after first and 7 days after latest dose of tralokinumab. The subject was hospitalised with worsening of atopic dermatitis on the whole body and was discharged 3 days after the onset of the SAE. The subject was treated with several topical treatments. IMP treatment was continued.

The event was considered not related to IMP by both the investigator and the sponsor and the outcome was reported as recovered after 5 days.

Maintenance treatment period (Week 16 to Week 52)

No SAEs were reported during the maintenance treatment period.

Open-label treatment period (Week 16 to Week 52)

7 SAEs were reported in 7 subjects (3.0%) receiving open-label treatment at a rate of 4.63 events per 100 PYE, which was comparable with the rate reported with tralokinumab 300 mg Q2W in the initial treatment period (3.39 events per 100 PYE) and lower than the rate reported with tralokinumab 150 mg Q2W in the initial treatment period (10.23 events per 100 PYE).

1 SAE ('gastritis') was considered related to IMP.

Panel 68 ***Overview of serious adverse events, open-label treatment: open-label safety analysis set***

System organ class Preferred term	Severity	Relation to IMP	Outcome	AESI
Psychiatric disorders				
Anorexia nervosa	Severe	Not related	Recovering/resolving	No
Obsessive-compulsive disorder	Moderate	Not related	Recovered/resolved	No
Suicidal ideation	Moderate	Not related	Recovered/resolved with sequelae	No
Gastrointestinal disorders				
Gastritis	Moderate	Possibly related	Recovered/resolved	No
Immune system disorders				
Anaphylactic reaction	Severe	Not related	Recovered/resolved	No
Infections and infestations				
Appendicitis perforated	Severe	Not related	Recovered/resolved	No
Injury, poisoning and procedural complications				
Concussion	Moderate	Not related	Recovered/resolved	No

AESI = adverse event of special interest; IMP = investigational medicinal product.

Description of SAEs reported in the treatment arms:

1 subject had a moderate 'gastritis' with hospitalisation 318 days after first and 6 days after latest dose of IMP. The subject was discharged 5 days after the onset of the SAE. The subject was treated with oxycodone, tapentadol, pantoprazole, and a combination preparation of aluminium hydroxide, magnesium hydroxide, magnesium trisilicate, and simethicone. The subject's risk factors for gastritis included occasional excessive alcohol consumption and excessive stress. IMP treatment was continued. The event was considered possibly related to IMP by the investigator, but was considered not related to IMP by the sponsor due to the subject's risk factors. The subject recovered after 10 days.

1 subject had a severe 'anaphylactic reaction' (reported term: 'anaphylaxis to tree nut') 302 days after first and 11 days after latest dose of IMP after ingesting a tree nut of unknown type.

1 subject had a severe 'appendicitis perforated' with hospitalisation 117 days after first and 6 days after latest dose of IMP. Concurrent AEs of 'appendicitis perforated' (reported term: 'sepsis, secondary to perforated appendicitis') and 'hyponatraemia' were reported. The subject underwent an appendicectomy. The subject recovered from the SAE and AEs and was discharged after 5 days.

1 subject had a moderate 'concussion' with hospitalisation 203 days after first and 7 days after latest dose of IMP as a result of being involved in a traffic accident (a car hit the subject while riding a bicycle).

1 subject had severe 'anorexia nervosa' during open-label treatment (146 days after first and 4 days after latest dose of IMP) and severe 'intentional overdose' during the safety follow-up period (432 days after first and 80 days after latest dose of IMP).

The subject had been followed by a specialist in eating disorders since more than a year. The eating disorder aggravated since approximately Day 146. At the scheduled visit on Day 211, the investigator referred the subject to the specialist in eating disorders, who offered the subject to be hospitalised the following week. Between Day 219 and Day 407, the subject had 4 hospitalisations, with intermittent at-home periods of at most 10 days. During this period, the following relevant concurrent non-serious AEs were reported: 'intentional self-injury', 'anxiety', 'family stress', 'insomnia', 'personality disorder', 'suicidal ideation', and 'depression'. On Day 407, the subject was transferred to the psychiatric department from which the subject was discharged on Day 420. The subject was re-admitted on Day 432 for the SAE 'intentional overdose' after swallowing 10 ibuprofen tablets. The subject recovered from the 'intentional overdose' after 7 days and was discharged on Day 438. IMP treatment was continued. Both events were considered not related to IMP by both the investigator and the sponsor. The outcome of 'anorexia nervosa' was reported as recovering.

1 subject had moderate 'obsessive-compulsive disorder' (reported term: 'worsening of obsessive-compulsive disorder') 345 days after first and 52 days after latest dose of IMP. The subject was hospitalised with a worsening of obsessive-compulsive disorder on Day 345. The increase in symptoms were noted since the lockdown due to the COVID-19 pandemic. The subject's symptoms improved during the hospital stay and the subject was recovered and discharged 21 days after the onset of the SAE. IMP treatment was continued. The event was considered not related to IMP by both the investigator and the sponsor.

1 subject had moderate 'suicidal ideation' (reported term: 'suicidal ideation due to concerns in the home') 302 days after first and 5 days after latest dose of IMP. During the visit on Day 283, the investigator noticed cuts on the subject's forearms and wrists (reported as AE 'intentional self-injury') and referred the subject to a psychiatrist. The subject was seen by a psychiatrist on Day 302 and reported with the SAE 'suicidal ideation'. The same day, the subject was admitted to hospital for further assessment and management and was discharged again later that day. The subject was followed up regularly and was formally diagnosed with major depression disorder and generalised anxiety disorder (reported as AEs 'depression' on Day 325 and 'generalised anxiety disorder' on Day 349). The subject started treatment with fluoxetine on Day 342. The subject had a family history of depression. IMP treatment was continued. The event was considered not related to IMP by both the investigator and the sponsor. The outcome was reported as recovered with sequelae (depression and generalised anxiety disorder) after 24 days.

Based on a recommendation from the DMC, an external paediatric psychiatrist reviewed all AEs in the SOC 'psychiatric disorders'. The conclusion of the report was that tralokinumab is considered safe and not contributing to mental illness in the exposed population, and no action was taken by the DMC as a result of the report.

Safety follow-up period (Week 52 to Week 66)

3 SAEs were reported in the safety follow-up period, in 3 subjects (1.5%) who had received open-label treatment (6.56 events per 100 PYE).

Panel 69 ***Overall summary of serious adverse events, safety follow-up period: safety follow-up analysis set***

System organ class Preferred term	Severity	Relation to IMP	Outcome	AESI
Tralokinumab 300 mg Q2W + TCS				
Immune system disorders				
Anaphylactic reaction	Severe	Not related	Recovered/resolved	No
Injury, poisoning and procedural complications				
Intentional overdose	Severe	Not related	Recovered/resolved	No
Renal and urinary disorders				
Renal injury	Severe	Not related	Recovered/resolved	No

AESI = adverse event of special interest; IMP = investigational medicinal product; Q2W = every 2 weeks; TCS = topical corticosteroid

1 subject who had received open-label treatment had a severe 'anaphylactic reaction' (reported term: 'food anaphylaxis') with hospitalisation 410 days after first and 61 days after latest dose of IMP after ingesting pesto containing pine nuts.

1 subject had severe 'anorexia nervosa' during open-label treatment (146 days after first and 4 days after latest dose of IMP) and severe 'intentional overdose' during the safety follow-up period (432 days after first and 80 days after latest dose of IMP).

1 subject who had received open-label treatment had a severe 'renal injury' (reported term: 'kidney lesion') with hospitalisation 399 days after first and 46 days after latest dose of IMP as a result of being involved in a car accident.

Adverse events of special interest

In this trial, the following AEs were predefined as AESIs.

- Eczema herpeticum.
- Malignancies diagnosed after randomisation.
- Skin infection requiring systemic treatment.
- Eye disorders (conjunctivitis, keratoconjunctivitis, and keratitis).

In total, 2 AESIs of 'eczema herpeticum', 24 AESIs of 'skin infection requiring systemic treatment', and 31 AESIs of 'eye disorders' were reported in the trial. No AESIs of 'malignancies diagnosed after randomisation' were reported in the trial

Eczema herpeticum

In total, 2 AESIs of 'eczema herpeticum' were reported in the trial, both in the initial treatment period: 1 event in 1 subject (1.0%) in the tralokinumab 150 mg Q2W group (3.41 events per 100 PYE) and 1 event in 1 subject (1.1%) in the placebo group (3.58 events per 100 PYE). Both events were non-serious. The event in the tralokinumab 150 mg Q2W group was moderate in severity and considered not related to IMP; the one in the placebo group was mild and considered related to IMP.

Skin infections requiring systemic treatment

Overall, the majority of AESIs of 'skin infections requiring systemic treatment' reported in the trial were non-serious and mild or moderate in severity. Approximately half of the events were assessed as related to the IMP, none of the events led to permanent discontinuation of IMP or to withdrawal from trial, and most of the subjects recovered from the events.

Initial treatment period (Week 0 to Week 16)

In the initial treatment period, AESIs of 'skin infections requiring systemic treatment' were infrequently reported.

Panel 70 ***Overall summary of adverse events of special interest – skin infections requiring systemic treatment, initial treatment period: safety analysis set***

	Tralokinumab 150 mg Q2W (n=98, PYE=29.33)				Tralokinumab 300 mg Q2W (n=97, PYE=29.48)				Placebo (n=94, PYE=27.93)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Events	5	(5.1)	7	23.86	2	(2.1)	3	10.18	2	(2.1)	2	7.16
Serious	1	(1.0)	1	3.41	0				0			
Severity												
Mild	3	(3.1)	3	10.23	1	(1.0)	1	3.39	1	(1.1)	1	3.58
Moderate	2	(2.0)	3	10.23	2	(2.1)	2	6.78	1	(1.1)	1	3.58
Severe	1	(1.0)	1	3.41	0				0			
Related to IMP *	2	(2.0)	4	13.64	2	(2.1)	2	6.78	0			
Leading to withdrawal	0				0				0			
Outcome												
Fatal	0				0				0			
Not recovered/Not resolved	0				0				0			
Recovering/Resolving	0				0				0			
Recovered/Resolved	5	(5.1)	7	23.86	2	(2.1)	3	10.18	2	(2.1)	2	7.16
Recovered/Resolved with sequelae	0				0				0			
Unknown	0				0				0			
Action taken with IMP												
Dose not changed	5	(5.1)	6	20.45	2	(2.1)	3	10.18	2	(2.1)	2	7.16
Dose reduced	0				0				0			
Dose increased	0				0				0			
Drug interrupted	1	(1.0)	1	3.41	0				0			
Drug withdrawn	0				0				0			
Not applicable	0				0				0			
Unknown	0				0				0			

AEs collected during the exposure time in the initial treatment period are shown.
AESI: Adverse event of special interest. Q2W: Every 2 weeks. IMP: Investigational medicinal product. PYE: Patient years of exposure.
n: Number of subjects in analysis set. N: Number of subjects with one or more events. %: Percentage of subjects with one or more events. E: Number of adverse events. R: Rate (number of events divided by patient years of exposure multiplied by 100).
*) Considered possibly or probably related to trial product by the investigator.

Maintenance treatment period (Week 16 to Week 52)

1 AESI of 'skin infections requiring systemic treatment' was reported during the maintenance treatment period: 1 non-serious and moderate AE of 'furuncle' on the lower limb was reported in 1 subject (16.7%) in the placebo group.

Open-label treatment period (Week 16 to Week 52)

9 AESIs of 'skin infections requiring systemic treatment' were reported in 7 subjects (3.0%) receiving open-label treatment at a rate of 5.96 events per 100 PYE, which was lower than the rate reported with tralokinumab Q2W in the initial treatment period (10.18 events per 100 PYE for tralokinumab 300 mg Q2W and 23.86 events per 100 PYE for tralokinumab 150 mg Q2W).

Safety follow-up period (Week 52 to Week 66)

2 AESIs of 'skin infections requiring systemic treatment' were reported in the safety follow-up period, both in subjects who had received open-label treatment.

Eye disorders

All events of 'eye disorders' reported in the trial were non-serious, all were mild or moderate in severity, approximately half of the events were assessed as related to IMP, and most of the subjects recovered from the events.

Most of the AESIs of 'eye disorders' were conjunctivitis; only 2 events of keratitis and no events of keratoconjunctivitis were reported.

No clinically relevant differences in the frequency of events of 'eye disorders' between the treatment groups and between the treatment periods were observed.

Initial treatment period (Week 0 to Week 16)

Panel 71 ***Summary of adverse events of special interest – eye disorders, initial treatment period: safety analysis set***

	Tralokinumab 150 mg Q2W (n=98, PYE=29.33)				Tralokinumab 300 mg Q2W (n=97, PYE=29.48)				Placebo (n=94, PYE=27.93)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Events	4	(4.1)	4	13.64	4	(4.1)	4	13.57	2	(2.1)	3	10.74
Serious	0				0				0			
Severity												
Mild	3	(3.1)	3	10.23	2	(2.1)	2	6.78	2	(2.1)	3	10.74
Moderate	1	(1.0)	1	3.41	2	(2.1)	2	6.78	0			
Severe	0				0				0			
Related to IMP *	1	(1.0)	1	3.41	1	(1.0)	1	3.39	1	(1.1)	2	7.16
Leading to withdrawal	0				0				0			
Drug withdrawn	0				0				0			
Classification												
Preferred term												
Conjunctivitis	4	(4.1)	4	13.64	3	(3.1)	3	10.18	2	(2.1)	3	10.74
Conjunctivitis	2	(2.0)	2	6.82								
Conjunctivitis bacterial					1	(1.0)	1	3.39				
Conjunctivitis allergic	2	(2.0)	2	6.82	2	(2.1)	2	6.78	2	(2.1)	3	10.74
Keratitis					1	(1.0)	1	3.39				
Keratitis viral					1	(1.0)	1	3.39				

AEs collected during the exposure time in the initial treatment period are shown.
Classification according to MedDRA 20.0. Q2W: Every 2 weeks. IMP: Investigational medicinal product. PYE: Patient years of exposure. n: Number of subjects in analysis set. N: Number of subjects with one or more events. %: Percentage of subjects with one or more events. E: Number of adverse events. R: Rate (number of events divided by patient years of exposure multiplied by 100). MedDRA: Medical Dictionary for Regulatory Activities.
*) Considered possibly or probably related to trial product by the investigator.

Maintenance treatment period (Week 16 to Week 52)

Overall, 3 AESIs of 'eye disorders' were reported in the maintenance treatment period.

All events were classified as conjunctivitis (preferred terms 'conjunctivitis' and 'conjunctivitis allergic').

Open-label treatment period (Week 16 to Week 52)

15 AESIs of 'eye disorders' were reported in 12 subjects (5.1%) receiving open-label treatment at a rate of 9.93 events per 100 PYE, which was comparable with the rate reported with tralokinumab Q2W in the initial treatment period (13.57 events per 100 PYE for tralokinumab 300 mg Q2W and 13.64 events per 100 PYE for tralokinumab 150 mg Q2W).

1 event was classified as keratitis (preferred term 'keratitis viral'), all other events were classified as conjunctivitis (preferred terms 'conjunctivitis', 'conjunctivitis bacterial', and 'conjunctivitis allergic'). No events classified as keratoconjunctivitis were reported.

Safety follow-up period (Week 52 to Week 66)

In the safety follow-up period, 2 AESIs of 'eye disorders' were reported, in 2 subjects (1.0%) who had received open-label treatment at a rate of 4.38 events per 100 PYE. Both events were non-serious and classified as conjunctivitis (preferred term 'conjunctivitis').

Comparison to adults

Panel 72 ***Summary of AEs of special interest - initial treatment period – AD pool vs ECZTRA 6 - adjusted pooling – safety analysis set***

	AD pool								ECZTRA 6							
	Tralokinumab 300 mg Q2W (n=1605, PYE=473.21)				Placebo (n=680, PYE=193.1)				Tralokinumab Q2W Total (n=195, PYE=58.81)				Placebo (n=94, PYE=27.93)			
	N	(adj.%)	E	adj.R	N	(adj.%)	E	adj.R	N	(%)	E	R	N	(%)	E	R
Adverse Events of Special Interest																
Eczema herpeticum	6	(0.3)	6	1.2	10	(1.5)	10	5.2	1	(0.5)	1	1.7	1	(1.1)	1	3.6
Malignancies diagnosed after randomisation	1	(0.1)	1	0.2	0				0				0			
Skin infections requiring systemic treatment	42	(2.6)	46	9.7	35	(5.5)	42	22.8	7	(3.6)	10	17.0	2	(2.1)	2	7.2
Eye disorders	132	(7.9)	155	31.1	22	(3.4)	24	12.9	8	(4.1)	8	13.6	2	(2.1)	3	10.7
- Conjunctivitis	126	(7.5)	145	29.0	21	(3.2)	23	12.3	7	(3.6)	7	11.9	2	(2.1)	3	10.7
- Keratoconjunctivitis	5	(0.3)	5	1.2	0				0				0			
- Keratitis	4	(0.2)	5	0.9	1	(0.2)	1	0.6	1	(0.5)	1	1.7	0			

AEs collected during the exposure time in the initial treatment period are shown. AE: Adverse event. Q2W: Every 2 weeks. PYE: Patient years of exposure. n: Number of subjects. N: Number of subjects with one or more events. %: Percentage of subjects with one or more events. E: Number of adverse events. R: Rate (number of events divided by patient years of exposure multiplied by 100). adj. %: Adjusted percentage calculated using Cochran-Mantel-Haenszel (CMH) weights. adj. R: Adjusted rate calculated using CMH weights.

Other adverse events of interest

As for the initial safety evaluation of tralokinumab in adults, other safety areas of interest were included in the evaluation of data from ECZTRA 6 based on pre-defined MedDRA search criteria. These were based on the known risks associated with administration of monoclonal antibodies, the understood mechanism of action of tralokinumab, AEs previously reported for other monoclonal antibodies, and regulatory interest. Other AEs of interest included:

- Anaphylaxis and serious allergic reactions.
- Immune complex disease.
- Injection site reactions.
- Severe or serious infections.
- Medication errors.
- Suicidality and psychiatric disorders.
- Rare adverse events.
- Cardiovascular events of interest.
- Malignancy

Panel 73 ***Summary of other AEs of interest - initial treatment period - AD pool vs ECZTRA 6 - adjusted pooling – safety analysis set***

	AD pool								ECZTRA 6							
	Tralokinumab 300 mg Q2W (n=1605, PYE=473.21)				Placebo (n=680, PYE=193.1)				Tralokinumab Q2W Total (n=195, PYE=58.81)				Placebo (n=94, PYE=27.93)			
	N	(adj.%)	E	adj.R	N	(adj.%)	E	adj.R	N	(%)	E	R	N	(%)	E	R
Other safety areas of interest																
Anaphylaxis and serious allergic reactions	8	(0.4)	8	1.5	4	(0.6)	4	2.1	1	(0.5)	1	1.7	2	(2.1)	2	7.2
- Anaphylaxis	0				0				0				0			
- Serious allergic reactions	8	(0.4)	8	1.5	4	(0.6)	4	2.1	1	(0.5)	1	1.7	2	(2.1)	2	7.2
Immune complex disease	0				1	(0.2)	1	0.6	0				0			
Injection site reactions	119	(7.2)	255	51.5	19	(3.0)	38	21.3	16	(8.2)	29	49.3	1	(1.1)	1	3.6
Serious infections	6	(0.4)	6	1.3	7	(1.1)	7	3.7	1	(0.5)	1	1.7	1	(1.1)	1	3.6
Severe infections (Any severe infection)	10	(0.6)	10	2.1	9	(1.4)	11	5.8	2	(1.0)	2	3.4	0			
Severe infections (Any infection requiring treatment with parenteral antibiotics)	8	(0.4)	9	1.7	5	(0.7)	5	2.5	1	(0.5)	1	1.7	2	(2.1)	2	7.2
Severe infections (Any infection requiring treatment with oral antibiotics/antivirals/ antifungal for more than 2 weeks)	15	(0.9)	15	3.2	14	(2.2)	15	8.3	7	(3.6)	9	15.3	2	(2.1)	3	10.7
Severe infections (Any clinical endoparasitosis)	0				0				0				0			
Severe infections (Any opportunistic infection)	56	(3.4)	64	13.0	32	(4.9)	40	21.3	6	(3.1)	7	11.9	3	(3.2)	4	14.3
Severe infections (Any tuberculous infection)	0				0				0				0			
Medication errors	15	(0.9)	20	4.0	5	(0.7)	5	2.5	2	(1.0)	2	3.4	0			
Suicidality	2	(0.1)	2	0.4	0				1	(0.5)	1	1.7	0			
Other																
Rare events	9	(0.6)	11	2.2	3	(0.4)	3	1.3	0				1	(1.1)	1	3.6
CV events of interest	0				0				1	(0.5)	1	1.7	0			
Malignancy (SMQ)	8	(0.5)	14	2.6	3	(0.4)	5	2.6	0				0			

AEs collected during the exposure time in the initial treatment period are shown. AE: Adverse event. Q2W: Every 2 weeks. PYE: Patient years of exposure. n: Number of subjects. N: Number of subjects with one or more events. %: Percentage of subjects with one or more events. E: Number of adverse events. R: Rate (number of events divided by patient years of exposure multiplied by 100). adj. %: Adjusted percentage calculated using Cochran-Mantel-Haenszel (CMH) weights. adj. R: Adjusted rate calculated using CMH weights.

Laboratory findings

Clinical laboratory evaluations are based on mean and potentially clinically significant values, shifts from baseline, and AEs.

Biochemistry

Overall summary of biochemistry parameters

The following biochemistry parameters were assessed in ECZTRA 6:

- Electrolytes: sodium, potassium, calcium.
- Renal function parameters: creatinine, urea nitrogen, albumin, protein.
- Lipids: cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides.
- Other biochemistry parameters: glucose (non-fasting), lactate dehydrogenase, immunoglobulin E.
- Liver parameters: ALP, AST, ALT, gamma glutamyl transferase, bilirubin.

Throughout the trial, the mean levels of most biochemistry parameters assessed in ECZTRA 6 were within the normal reference range at baseline and the mean and mean changes showed only minor fluctuations

within the normal reference ranges. There were no clinically relevant differences between treatment groups. In line with the observations in the adult pools, no clinically relevant changes in biochemistry parameters (electrolytes, renal and liver function parameters, and lipids) were observed, based on the evaluation of means, values deemed PCS, and AEs.

Liver parameters

No cases of potential drug-induced liver injury (concurrent elevations of ALT or AST ≥3× ULN and bilirubin ≥2× ULN) were identified in ECZTRA 6.

In line with the observations in the AD pool in adults (ECZTRA trials only) the incidences of PCS liver abnormalities in ECZTRA 6 were low:

- PCS ALT levels (all between 3× and 5× ULN) were observed in 2 subjects receiving tralokinumab (150 mg Q2W initial treatment, and 300 mg Q2W open-label treatment).
- PCS AST levels (between 10× and 20× ULN) were observed in 1 subject receiving tralokinumab (150 mg Q2W initial treatment).
- PCS ALP levels (>1.5× ULN) were observed in 9 subjects receiving tralokinumab (300 mg Q2W initial or open-label treatment) and in 5 subjects off-treatment (who had received tralokinumab 300 mg Q2W open-label treatment).
- No PCS liver abnormalities were observed in the placebo groups.

The safety profile of subjects with PCS liver parameter values was comparable with that of the total trial population. For most of the cases, no AE related to the increased value was reported, i.e. the increases were not considered clinically significant by the investigator. There was no pattern or clustering of the type of AEs reported for these subjects.

Throughout ECZTRA 6, few cases of liver parameters above the ULN were considered clinically significant and thus reported as AEs.

Such AEs were only reported in the tralokinumab groups; all were mild in severity, and none led to discontinuation of the IMP. All events resolved during the trial except for an AE of hyper-bilirubinaemia reported off-treatment, which was resolving by the end of the trial reported. As was the case for the AD pool, none of these AEs were reported as SAEs.

Based on the above, it can be concluded that, as for the adult population, no clinically relevant changes in liver or hepatobiliary parameters were observed in the adolescent population in ECZTRA 6. No tralokinumab-induced cases of Hy's law or drug-induced liver injury were identified.

Haematology

Overall summary of haematology parameters

The following haematology parameters were assessed in ECZTRA 6:

- Red blood cells: erythrocytes, haematocrit, haemoglobin, erythrocyte mean corpuscular haemoglobin concentration, and erythrocyte mean corpuscular volume.
- Platelets: thrombocytes.
- White blood cells: basophils, basophils/leukocytes, lymphocytes, lymphocytes/leukocytes, monocytes, monocytes/leukocytes, neutrophils, neutrophils/leukocytes, eosinophils, eosinophils/leukocytes, and leukocytes.

Throughout ECZTRA 6, the mean and mean changes of most haematology parameters showed only minor fluctuations within the normal reference ranges, except for eosinophils and eosinophil/leukocyte counts. There were no clinically relevant differences between treatment groups.

In line with the observations in the adult pools, no clinically relevant changes in red blood cells or associated parameters, platelets, or white blood cells (with the exception of eosinophils) were observed, based on the evaluation of means, PCS values, and AEs.

Eosinophils

More than 40% of the subjects in each treatment group in ECZTRA 6 had baseline eosinophil levels above the ULN (>0.5×10^9/L). These data were consistent with those in the adult pools. As also observed in the AD pool, there was a transient increase in eosinophil levels in the tralokinumab groups in ECZTRA 6. Mean changes from baseline were similar in ECZTRA 6 and the AD pool, and were at most around 0.2×10^9/L.

Figure 7 ***Mean change from baseline plot of eosinophils over time - entire trial period – ECZTRA 6 - safety analysis set***

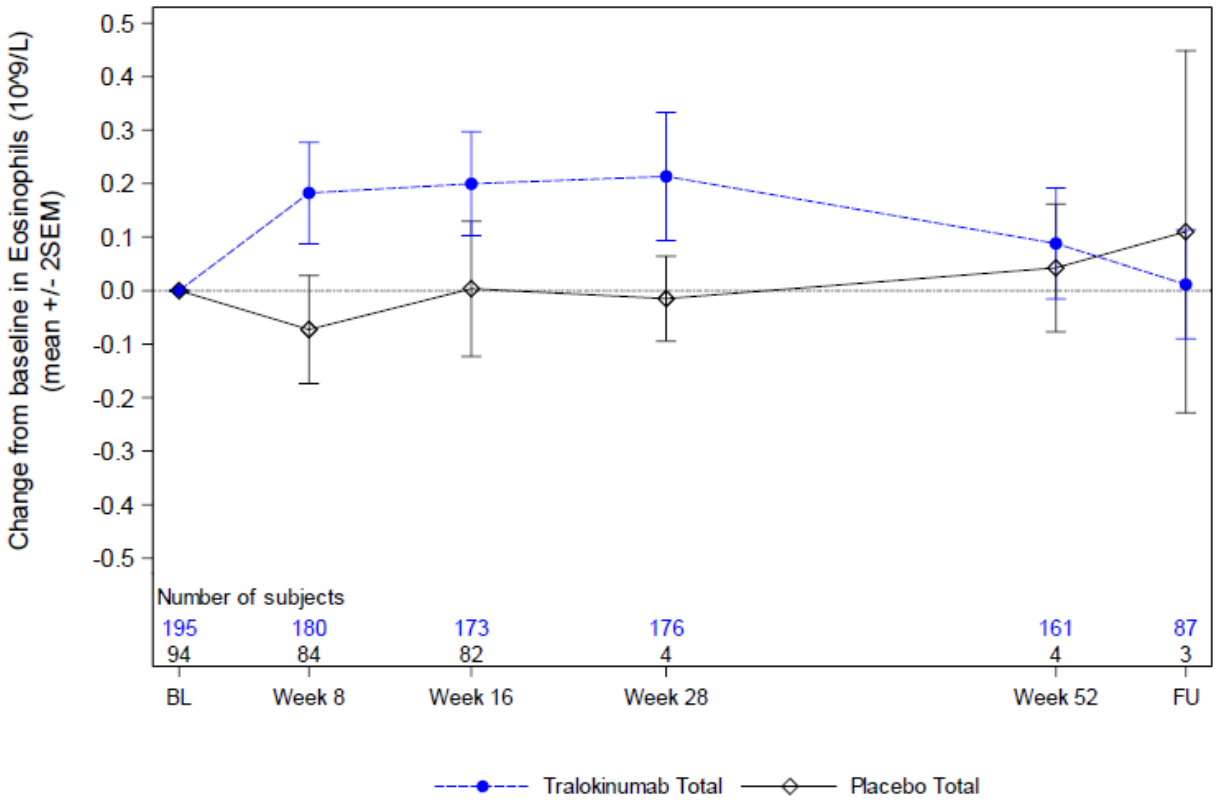
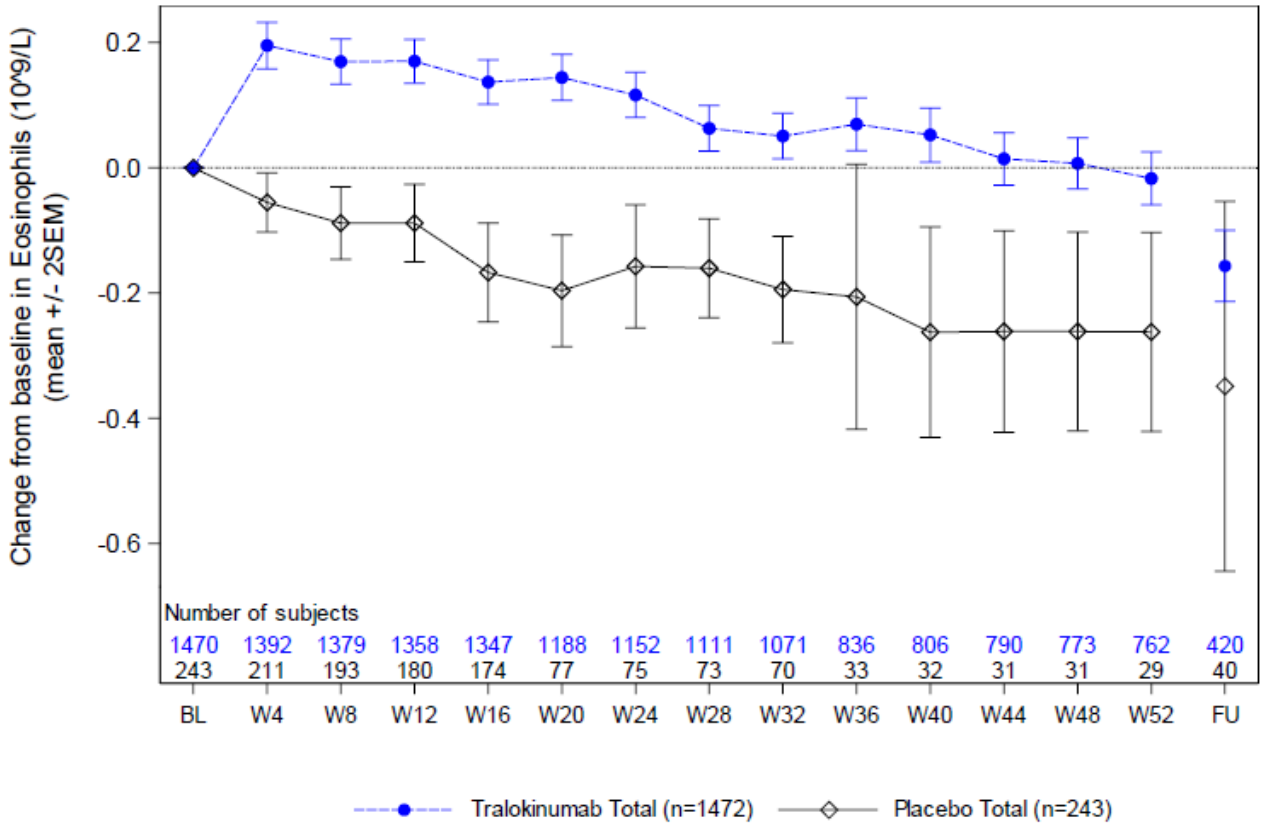


Figure 8 ***Mean change from baseline plot of eosinophils over time - entire treatment period - AD pool (ECZTRA trials only) - safety analysis set***



The incidence of PCS eosinophil levels >1.5×10^9/L (including levels between 1.5×10^9/L and 5.0×10^9/L and levels >5.0×10^9/L) during the treatment periods was lower in ECZTRA 6 than in the AD pool and monotherapy pool

Panel 74 ***Incidence of PCS eosinophil levels - AD pool and monotherapy pool vs ECZTRA 6***

Eosinophil levels	AD / monotherapy pool[a] (adults)			ECZTRA 6 (adolescents)				
	Tralokinumab n (%)		Placebo n (%)	Tralokinumab 150 mg n (%)		Tralokinumab 300 mg n (%)		Placebo n (%)
Initial treatment period								
Regimen	Q2W		Q2W	Q2W		Q2W		Q2W
N	1553		629	98		97		94
>1.5×10^9/L – ≤5.0×10^9/L	346 (22.3%)		59 (9.4%)	14 (14.3%)		12 (12.4%)		4 (4.3%)
>5.0×10^9/L	19 (1.2%)		2 (0.3%)	2 (2.0%)		1 (1.0%)		0
Maintenance treatment period								
Regimen	Q2W	Q4W	Q2W	Q2W	Q4W	Q2W	Q4W	Q2W
N	159	165	81[b] / 60[c]	12	14	11	13	6
>1.5×109/L – ≤5.0×109/L	22 (13.8%)	22 (13.3%)	9 (11.1%)[b] 2 (3.3%)[c]	1 (8.3%)	0	1 (9.1%)	0	0
>5.0×109/L	0	0	0	0	0	0	0	0
Open-label treatment period								
Regimen	Q2W		-	-		Q2W		-
N	1121		-	-		234		-
>1.5×109/L – ≤5.0×109/L	298 (26.6%)		-	-		35 (15.0%)		-
>5.0×109/L	9 (0.8)		-	-		2 (0.9%)		-

No AEs of 'eosinophilia' or 'eosinophil count increased' were reported in ECZTRA 6. Consistent with the observations in the AD pool and monotherapy pool the safety profile of subjects with elevated eosinophil

levels (>1.5×10^9/L) was comparable with that of the total trial population. There was no pattern or clustering of the type of AEs reported for subjects with elevated eosinophil levels and no events raised concerns for a causal relationship to the eosinophil count. Although no eosinophilia-related AEs were reported in ECZTRA 6, eosinophilia is considered an ADR in adolescents – as is also the case in adults – based on the clinical laboratory findings for eosinophils in this trial.

Anti-drug antibodies

Serum samples for determination of presence or absence of ADA were collected at Weeks 0,4, 16, 28, 52, and 66.

The majority of subjects did not develop anti-tralokinumab antibodies or nAB. In total, 1 subject (1.0%) in the tralokinumab 300 mg Q2W group, 7 subjects (7.1%) in the tralokinumab 150 mg Q2W group, and 2 subjects (2.1%) in the placebo group were tested positive for ADA at any time point post-baseline during the initial treatment period.

During the entire trial (including the safety follow-up period), there were 22 subjects (8.0%) who had a positive ADA status after initiation of treatment with tralokinumab. Among tralokinumab-naïve subjects (i.e. subjects not exposed to tralokinumab prior to ADA assessment), a positive ADA status was observed for 2 subjects (2.1%).

Panel 75 ***Anti-drug antibodies, entire trial including safety follow-up: safety analysis set***

	Subjects treated with Tralokinumab + TCS (n=275)		Tralokinumab naive# subjects (n=94)		Safety Analysis Set Total (n=288)	
ADA status	N	(%)	N	(%)	N	(%)
Positive	22	(8.0)	2	(2.1)	24	(8.3)
Pre-existing*	1	(0.4)			1	(0.3)
Treatment-boosted**	1	(0.4)			1	(0.3)
Treatment emergent***	20	(7.3)	2	(2.1)	22	(7.6)
Persistent$	4	(1.5)			4	(1.4)
Indeterminate$$	10	(3.6)	2	(2.1)	10	(3.5)
Transient$$$	6	(2.2)			8	(2.8)
Perishing~	7	(2.5)	1	(1.1)	5	(1.7)
Negative~~	242	(88.0)	89	(94.7)	254	(88.2)
No post-baseline ADA assessment	4	(1.5)	2	(2.1)	5	(1.7)

ADA: Anti-drug antibodies. n: Number of subjects in analysis set. N: Number of subjects with observation. %: Percentage of subjects. Q2W: Every 2 weeks.
#) Subjects not exposed to tralokinumab prior to ADA assessment.
*) ADA positive at baseline, no post-baseline ADA response greater or equal to 4-fold over baseline titer level. At least one non-missing post-baseline ADA assessment.
**) ADA positive at baseline, at least one post-baseline ADA response greater or equal to 4-fold over baseline titer level.
***) ADA negative or missing at baseline, at least one positive post-baseline ADA response.
$) Positive ADA for at least 2 consecutive visits at least 10 weeks apart.
$$) Only the last ADA response positive.
$$$) Neither persistent nor indeterminate.
~) ADA positive at baseline, all post-baseline ADA assessments negative.
~~) ADA negative or missing at baseline, all post-baseline ADA assessments negative.

In ECZTRA 6, the proportions of subjects with treatment-emergent ADA were marginally higher than those reported for the adult population. However, ADA titres and the presence of neutralising antibodies were similarly low and were deemed not to have an impact on the pharmacokinetics, efficacy, or safety of tralokinumab.

Panel 76 ***Anti-drug antibodies in ECZTRA 6 and ADA ECZTRA analysis set***

Trial period ADA status	ECZTRA 6 (adolescents)			ADA ECZTRA analysis set[a] (adults)	
Initial treatment	Tralokinumab		Placebo (N=94)	Tralokinumab 300 mg (N=1553)	Placebo (N=629)
	150 mg (N=98)	300 mg (N=97)			
Treatment-emergent[b]	7 (7.1%)	0	2 (2.1%)	21 (1.4%)	8 (1.3%)
Entire trial	**Tralokinumab-treated (N=275)**		**Tralokinumab-naïve (N=94)**	**Tralokinumab-treated (N=1939)**	**Tralokinumab-naïve (N=629)**
Treatment-boosted[c]	1 (0.4%)			3 (0.2%)	
Treatment-emergent[b]	20 (7.3%)		2 (2.1%)	87 (4.5%)	9 (1.4%)
Persistent[d]	4 (1.5%)			17 (0.9%)	1 (0.2%)

Note: a = all subjects treated in the ECZTRA 1, 2, 3, and 5 trials; **b** = ADA-negative or missing at baseline and at least 1 positive post-baseline ADA response; **c** = ADA-positive at baseline and at least 1 post-baseline ADA response ≥4-fold over baseline titre level; **d** = ADA-positive for at least 2 consecutive visits at least 10 weeks apart.

Vital signs, physical findings, and other observations related to safety

Consistent with the observations in the adult population no findings related to vital signs, physical examination, or ECG in ECZTRA 6 gave rise to any safety concerns.

Digital ECG

Overall, no clinically relevant changes in ECG parameters were observed during the entire treatment period. Only 1 subject shifted from a 'normal' or 'abnormal, not clinically significant' ECG evaluation at baseline to an 'abnormal, clinically significant' ECG evaluation during the treatment period. 4 AEs related to ECG were reported (during open-label treatment), all non-serious and mild or moderate in severity, of which 2 were considered related to IMP.

During open-label treatment, 4 AEs related to ECG were reported in 3 subjects: 'tachycardia', 'electrocardiogram QT prolonged', and 2 events of 'heart rate increased' (both in the same subject, of which 1 was reported as 'temporary elevation of heart rate after IP' on a day of IMP administration).

Safety in special groups and situations

Intrinsic and extrinsic factors

The potential effects of intrinsic and extrinsic factors on the safety profile of tralokinumab in adolescent subjects were investigated based on AE data from the initial treatment period in ECZTRA 6, assessed by the following subgroups: sex, race, age, body weight, baseline IGA, and region.

In line with the observations in the monotherapy pool in adults, no clinically relevant differences between subgroups in ECZTRA 6 were identified after evaluation of AE summaries (overall incidence, event number/rate, causality, severity, and seriousness) and the AE distribution by SOC and PT. Furthermore, no differences in the incidences of SAEs were observed across the subgroups. Overall, the AE profile and AE distribution by SOC and PT were comparable across subgroups and resembled those observed for the total trial population and there are no indications that intrinsic or extrinsic factors affect the safety profile of

tralokinumab in adolescent subjects. As expected from multiple comparisons, however, as well as from variations in reporting practices across different demographic subgroups and across different regions, minor variations in the reporting of AEs were observed across some of the demography subgroups. This is also in line with the observations in the monotherapy pool in adults.

Use in pregnancy and lactation

In the 2 completed trials and 1 ongoing trial with tralokinumab in adolescent subjects, 1 pregnancy has been reported prior to the data cut-off (31-Mar-2021).

Panel 77 ***Pregnancy reported in adolescent subject treated with tralokinumab***

Pregnancy reported in an adolescent subjects treated with tralokinumab	
Trial ID	ECZTEND
Treatment regimen	ECZTRA 6: tralokinumab 300 mg Q2W → tralokinumab 300 mg Q2W open-label → ECZTEND: tralokinumab 300 mg Q2W open-label
Age	16 years
Trial period when pregnancy occurred	Treatment period
Maternal / Paternal	Maternal
Pregnancy outcome	Elective abortion
Obstetric history	None
Contraception	Condom
Permanent discontinuation of IMP	Yes
Event description	The subject became pregnant on an unknown date while participating in ECZTEND. The subject did not plan to continue the pregnancy and had an elective abortion in week 7 of the pregnancy. IMP was discontinued 34 days before the abortion.

Owing to the limited number of pregnancies in both adult and adolescent subjects exposed to tralokinumab to date, the current data are not considered sufficient to inform about the pregnancy risks associated with tralokinumab exposure. Nevertheless, the available data from the clinical trials and nonclinical studies to date do not suggest that tralokinumab has an adverse effect on pregnancy or pregnancy outcomes.

Overdose

No overdose of IMP was reported in ECZTRA 6.

Safety related to drug-drug interactions and other interactions

A type II C.I.4 variation was submitted to update the SmPC with inclusion of the drug-drug interaction data on 27 September 2021 with corresponding procedure start 18 October 2021. As this variation is ongoing the proposed changes to the PI with this adolescent variation, do not contain the proposed changes for the C.I.4 drug-drug interaction variation.

Discontinuation due to adverse events

Overall, AEs leading to permanent discontinuation of IMP and/or withdrawal from the trial were reported with low frequencies in the entire trial and no clinically relevant difference between treatment groups was observed. In total, 3 AEs led to permanent discontinuation of IMP, 1 event in the initial treatment period and 2 events with open-label treatment. 1 event was serious, severe, and considered not related to IMP. The other 2 were non-serious and considered related to IMP.

1 AE led to permanent discontinuation of IMP and to withdrawal from trial during the initial treatment period: the AE 'cerebrovascular accident' reported in a subject in the tralokinumab 150 mg Q2W group. The event was serious, severe, and considered not related to IMP.

2 AEs in 2 subjects (0.9%) led to permanent discontinuation of IMP and to withdrawal from trial in subjects receiving open-label treatment:

- an AE of 'foreign body sensation in eyes', which was non-serious, moderate in severity, and considered possibly related to IMP. The subject had not recovered from the event by the end of the trial.
- an AE of 'procedural anxiety', which was non-serious, moderate in severity, and considered probably related to IMP. The subject had recovered from the event by the end of the trial.

Post marketing experience

At the time of submission of this application to extend the indication to adolescents, tralokinumab had only been approved for adults and had only been launched in 1 country to date (Germany, since mid-July 2021) after it was first approved in EU on 17-Jun-2021. This limited post-marketing experience did not indicate any new safety concerns with tralokinumab in adults.

SmPC updates

The following update to the SmPC (section 4.8) is being proposed:

Adolescents

The safety of tralokinumab was assessed in a study of 289 patients 12 to 17 years of age with moderate-to-severe atopic dermatitis (ECZTRA 6). The safety profile of tralokinumab in these patients followed through the initial treatment period of 16 weeks and the long-term period of 52 weeks was similar to the safety profile from studies in adults.

Description of selected adverse reactions

In the adolescent trial, conjunctivitis occurred in 1.0% of atopic dermatitis patients treated with tralokinumab and in no patients treated with placebo in the initial treatment period of 16 weeks.

Conjunctivitis allergic occurred at similar frequency in atopic dermatitis adolescent patients, who received tralokinumab (2.1%) compared to placebo (2.1%) in the initial treatment period of 16 weeks.

2.5.1. Discussion on clinical safety

The data supporting the use of tralokinumab in adolescents derive from 1 pivotal trial and 2 supportive trials:

Pivotal trial:

- ECZTRA 6 – a completed phase 3 trial in adolescent subjects with moderate-to-severe AD who received tralokinumab (150 mg or 300 mg) or placebo for up to 52 weeks. This study is the primary source of new safety data included in this application.

Supportive trials:

- ECZTEND – an ongoing phase 3 extension trial in subjects with moderate-to-severe AD, including adolescent subjects who completed ECZTRA 6. As this trial is ongoing, only information on exposure, SAEs, and AEs leading to permanent discontinuation of IMP for the adolescent subjects

transferred from ECZTRA 6 were provided in this application as additional long-term safety data. The data cut-off for the safety data from ECZTEND was 31-Mar-2021.

- CD-RI-CAT-354-1054 – a completed phase 1 trial in adolescent subjects with asthma who received a single dose of tralokinumab 300 mg.

The design of ECZTRA 6 study was similar to the design of pivotal studies supporting the original MAA. In this study, there was an initial treatment period of 16 weeks and a maintenance treatment period of 36 weeks in subjects who obtained a clinical response at Week 16. Non-responders or subjects who lost their response were transferred to the open-label treatment period where their received tralokinumab 300 mg Q2W with optional use of TCS and/or TCI. In the study, there was also safety follow-up period (Week 52 to Week 66).

A number of dosing regimens were tested in the ECZTRA 6 study i.e 300 mg Q2W and 150 mg Q2W in the initial treatment period and 300 mg Q2W, 300 mg Q4W, 150 mg Q2W and 150 mg Q4W in the maintenance treatment period.

Patient exposure

In total 423 adolescents were exposed to tralokinumab in three clinical trials provided in support this application. 276 out of these 423 subjects were exposed to tralokinumab in ECZTRA 6 trial which is the primary source of new safety data for this application. In ECZTRA 6, 166 (60.1%) of the subjects were exposed to tralokinumab for 52 weeks or more; the corresponding number for placebo was 4 (4.3%) subjects. A majority of the remaining subjects were exposed to tralokinumab for at least 36 weeks, reflecting that most subjects who received placebo during the initial 16 weeks were subsequently transferred to open-label treatment with tralokinumab 300 mg Q2W. It is noted that only a few subjects with a long-term exposure received tralokinumab as monotherapy.

In the **ECZTRA 6 study,** in the **initial treatment period**, the incidence of AEs was slightly higher with tralokinumab 150 mg Q2W (67.3%) than with tralokinumab 300 mg Q2W (64.9%) and placebo (61.7%). 9 SAEs were reported in the initial treatment period i.e 1 event in the tralokinumab 300 mg Q2W, 3 in the tralokinumab 150 mg Q2W group and 5 in the placebo group.

The majority of reported AEs were mild. Severe AEs were reported only in 5.1% of subjects in the tralokinumab 150 mg Q2W group, 3.1% of subjects in the tralokinumab 300 mg Q2W groups and 7.4% of subjects in the placebo group.

Overall, AE incidences and rates observed during the initial treatment period in ECZTRA 6 were consistent with those seen in the AD pool in adults.

The frequency of AEs reported in the maintenance treatment period varied between the groups with the highest frequency in the placebo group and lowest in the tralokinumab 300 mg Q4W group. No SAEs were reported in the maintenance treatment period. Except for 1 severe AE reported in the tralokinumab 300 mg Q2W/Q2W group, all AEs were mild or moderate in severity.

In the maintenance treatment period AEs were overall reported at a lower rate for tralokinumab Q2W compared with tralokinumab Q2W in the initial treatment period.

However, the safety data for the **maintenance treatment period** should be interpreted with caution due to the low number of subjects in each treatment group (ranging from 11-14 subjects in the tralokinumab groups and 6 subjects in the placebo group).

67.5% of subjects enrolled to the **open label treatment period** reported AEs. However, the rate of AEs for subjects treated with open-label treatment was lower than the rate of AEs in the initial treatment period (349.4 events per 100 PYE in the open label period versus 441.0 events per 100 PYE with tralokinumab 300 mg Q2W and 596.6 events per 100 PYE with tralokinumab 150 mg Q2W in the initial treatment period).

The majority of AEs reported were mild. Severe AEs were reported in 4 subjects. 7 SAEs were reported in 7 subjects at a rate of 4.63 events per 100 PYE in subjects receiving open-label treatment and the rate was comparable with the rate of SAEs in the initial treatment period. There were 2 AEs that led to permanent discontinuation of IMP.

In general, it can be concluded that no apparent increase in the frequency of AEs overtime and the rate of AEs for subjects treated with the open-label treatment was lower than the rate of AEs in the initial treatment period.

Common AEs

In all treatment periods (i.e initial, maintenance and open label), the SOC with the highest incidence and rate of AEs were 'infections and infestations', 'skin and subcutaneous tissue disorders', and 'general disorders and administration site conditions'.

In the initial treatment period viral upper respiratory tract infection, dermatitis atopic, and upper respiratory tract infection were the most frequently reported AEs in all treatment groups.

Viral upper respiratory tract infection, upper respiratory tract infection, injection site reaction, injection site pain, nausea, dyspepsia and headache were reported with the higher frequency and with higher rate as compared to placebo. Upper respiratory tract infections and injection site reactions are listed in the SmPC.

The incidence and rate of AEs in the SOC 'psychiatric disorders' were higher in the tralokinumab groups as compared to the placebo group however the majority of preferred terms within this SOCs were single events. There was no apparent increase in the incidence and rate of AEs in the SOC of 'eye disorders'.

In general, in the maintenance treatment period and open-label treatment period types of AEs reported were similar to those reported during the initial treatment period. Again, viral upper respiratory tract infection' and 'upper respiratory tract infection were most frequently reported. There is no apparent increase in the frequency and rate of any type of AEs including injection site reactions.

The distribution patterns of AEs across SOCs and PTs observed in ECZTRA 6 were generally similar to the patterns observed in adults, except for lower incidences and rates in ECZTRA 6 for AEs reported in the SOC 'skin and subcutaneous tissue disorders' (mainly driven by the PT 'dermatitis atopic') and for the PT 'conjunctivitis'.

Related AEs

In general, during the initial treatment period in ECZTRA 6, the frequency and the rate of the related AEs was higher in the tralokinumab groups (26.5% for 150 mg Q2W and 25.8% for 300 mg Q2W) than for the placebo group (21.3%). The incidence and rate of related AEs in the SOC 'general disorders and administration site conditions was the highest. For injection site reactions a few preferred terms were reported including injection site reaction, injection site pain, injection site oedema, swelling and urticaria. In the maintenance treatment period and open-label treatment period related AEs were similar to those reported during the initial treatment period.

Adverse events by severity

Overall, the vast majority of AEs reported in the trial were mild or moderate in severity. In total, 31 severe AEs were reported, 21 events in the initial treatment period, 1 event in the maintenance treatment period, 4 events in subjects receiving open-label treatment, and 5 events in the safety follow-up period.

Serious adverse event/deaths/other significant events

No deaths were reported during the ECZTRA 6 trial.

Overall, SAEs were reported with low frequencies in all treatment groups in the entire trial and no pattern in SOCs or preferred terms was apparent. In total, 19 SAEs were reported: 9 in the initial treatment period (4 in the treatment arms), 7 with open-label treatment, and 3 in the safety follow-up treatment period. All SAEs were moderate or severe, all except for 1 SAE were assessed as not related to IMP by the investigator. 1 subject had a moderate 'gastritis' with hospitalisation 318 days after first and 6 days after latest dose of IMP. The event was considered possibly related to IMP by the investigator, but was considered not related to IMP by the sponsor due to the subject's risk factors.

The following SAEs required further discussion from the applicant:

Cerebrovascular accident

1 subject in the tralokinumab 150 mg Q2W group had a severe 'cerebrovascular accident' (reported term: 'stroke') with hospitalisation 57 days after first dose of tralokinumab, which is an unusual finding in adolescents. Cases of stroke and TIA were reported in the adult clinical studies and this issue was discussed during the original MAA.

The applicant considered that the occurrence in ECZTRA 6 of a single cardiovascular event with confounding factors did not change the evaluation from the original MAA that treatment with tralokinumab is not associated with a higher risk of cardiovascular events. This was accepted. The applicant was requested to present any further cases of cardiovascular events seen in adolescents in PSUR.

Suicidal ideation

During the initial treatment period in both ECZTRA 6 and the AD pool, suicidality events were only reported in the tralokinumab groups, albeit at a very low incidence (1 subject [1 event] in ECZTRA 6 and 2 subjects [2 events] in the AD pool).

AD is associated with numerous psychiatric comorbidities, including depression and anxiety. AD is associated with an increase in proinflammatory cytokines, and an association between pro-inflammatory responses and depression and suicidality has been hypothesised (the 'cytokine hypothesis'). There is no specific signal of increased risk of suicide by blocking IL-13 but since a diagnosis of AD is associated with a higher risk of depression and suicide, subjects who had a history of attempted suicide or were considered at significant risk of suicide attempt were excluded from the trial.

AESIs

In **ECZTRA 6**, the following AEs were predefined as AESIs: eczema herpeticum, malignancies diagnosed after randomisation, skin infection requiring systemic treatment and eye disorders (conjunctivitis, keratoconjunctivitis, and keratitis).

In total, 2 AESIs of 'eczema herpeticum (1 in the treatment arm) were reported.

24 AESIs of skin infection requiring systemic treatment were reported in ECZTRA 6. The rate of skin infection requiring systemic treatment in the initial treatment period was higher in the tralokinumab groups (23.86% for 150 mg Q2W and 10.18% for 300 mgQ2W) as compared to the placebo group (7.16%). In addition, the rate of skin infection requiring systemic treatment was higher in adolescents as compared to the AD pool in adults.

31 AESIs of 'eye disorders' were reported in the trial. Most of the AESIs of 'eye disorders' were conjunctivitis; only 2 events of keratitis and no events of keratoconjunctivitis were reported. The rate of conjunctivitis was slightly higher in the 150 mg Q2W group than in the placebo group. Conjunctivitis is listed in the SmPC. There was no increase in the rate of eye disorders in ECZTRA 6 as compared to the AD pool in adults.

No AESIs of 'malignancies diagnosed after randomisation' were reported in the trial.

As for the initial safety evaluation of tralokinumab in adults, other safety areas of interest in ECZTRA 6 included: anaphylaxis and serious allergic reactions, immune complex disease, injection site reactions, severe or serious infections, medication errors, suicidality and psychiatric disorders, rare adverse events, cardiovascular events of interest and malignancy.

For these no imbalances were observed between ECZTRA 6 and the AD pool with exception of the incidence of severe infections requiring treatment with oral antibiotics/antivirals/antifungal for more than 2 weeks for which the higher rate was reported in ECZTRA 6 for tralokinumab 150 mg Q2W as compared to the AD pool**.**

Discontinuation due to adverse events

Overall, AEs leading to permanent discontinuation of IMP and/or withdrawal from the trial were reported with low frequencies in the entire trial and no clinically relevant difference between treatment groups was observed in the initial treatment period (cerebrovascular accident) in addition to the 2 events with open-label treatment (foreign body sensation in eyes and procedural anxiety).

Safety of doses tested

In relation to the safety results in the initial treatment period, no major differences between doses were noted although slightly better results were reported unexpectedly for the higher dose (300 mg Q2W). AEs were reported in 67.3% of subjects in the 150 mg Q2W group and 64.9% of subjects in the 300 mg Q2W group. SAEs were reported in 3.1% and 1% of subjects in 150 mg Q2W and 300 mg Q2W groups, respectively. Severe AEs were reported in 5.1% in the 150 mg Q2W group and 3.1% of subjects in the 300 mg Q2W group. For the maintenance treatment period the number of subjects was too small to allow for firm conclusion.

ECZTEND trial

The safety data for adolescents who entered ECZTEND trial are very limited. It is noted that 1 SAE had been reported for an adolescent subject in this trial prior to the data cut-off date. The SAE was a mild event of 'hypertension'. The investigator considered the association between the SAE and the IMP unlikely but could not exclude it. The sponsor considered the SAE not related to the IMP and more likely explained by a recent COVID-19 infection. In addition, in this trial there was one AE leading to permanent discontinuation of IMP.

The Applicant has not submitted an updated RMP with this application. This is considered to be acceptable by the Rapporteur.

2.5.2. Conclusions on clinical safety

No major issues in relation to safety were identified.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative(s) of MS HU, MT and SI.

2.6.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

the updates to the Package Leaflet are very minor (added only that the information is relevant also for adolescent patients). No updates have been proposed to the Instruction for Use as no changes to the dose and the syringe have been made with this update. Adolescent patients were included in the Human Factor Study (provided with the initial MAA submission). The Human Factor Study demonstrated that adolescent patients were able to use the pre-filled syringe and understand the Instructions for Use.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Atopic dermatitis is the most common inflammatory skin disease in the developed world. It is more common in paediatric populations than in adults, with the 1-year prevalence in adolescents estimated to be approximately 15–20%. Although AD usually presents as mild disease in the paediatric population, around 10–30% of children with AD have moderate-to-severe disease.

Disease signs and symptoms in moderate-to-severe AD are characterised by intense itch, xerosis, and recurrent eczematous skin lesions. In children from 2 years of age to puberty, AD typically involves the flexural surfaces of the extremities, head, neck, wrists, and ankles.

In adolescents and adults, eczematous changes are typically seen on the head and neck, flexural surfaces of the extremities, and hands and feet. These signs and symptoms cause substantial morbidity and have a serious impact on the psychological wellbeing and health-related quality of life in affected children and their families. Compared with adolescents who do not have AD, adolescents with AD are at higher risk of the most common psychiatric conditions, including depression and anxiety, and this risk increases with increasing AD severity. Furthermore, children with AD are at higher risk of learning disabilities – with potential lifelong implications for health, educational, and social outcomes – and this risk also increases with increasing AD severity. An important treatment goal for patients in this vulnerable period of life is therefore to also improve their psychosocial wellbeing and ability to function in daily life.

3.1.2. Available therapies and unmet medical need

Standard treatment for AD in adolescents is similar to that in adults, typically progressing in accordance with disease severity from mild topical anti-inflammatory therapy to high-potency topical therapy and in some cases systemic immunomodulatory therapy.

TCS and TCI have limited efficacy in patients with moderate-to-severe disease. High-potency TCS, as well as systemic therapies except for the newer biologics and JAK inhibitors, are reserved for severe disease and are associated with significant safety concerns, especially in children and when used long-term. Cyclosporine, for instance, has common and severe side effects such as nephrotoxicity, hepatotoxicity, and

hypertension. Cyclosporine is therefore only approved for the treatment of severe AD and is only recommended for patients where the expected clinical benefit outweighs the risk of side effects. Some drugs in the JAK inhibitor drug class, including upadacitinib and ruxolitinib, have a black box warning by the FDA about increased risk of serious infections, heart-related events, cancer, blood clots, and death.

As AD is a heterogenous, chronic disease characterised by flares and exacerbations, multiple treatment options are necessary for adequate long-term disease management. Dupilumab is currently the only selective immunomodulating biologic therapy available for the treatment of AD in adolescents. However, some patients have inadequate response or unacceptable side effects with dupilumab. Hence, there is a need for additional well-tolerated treatments that target the underlying cause of AD and offer long-term disease control without intolerable side effects.

3.1.3. Main clinical studies

The data supporting the use of tralokinumab in adolescents derive from 1 pivotal trial and 2 supportive trials, as outlined below. The trials were conducted in accordance with the ICH guidance on GCP (ICH E6).

Pivotal trial:

- ECZTRA 6 – a completed phase 3 trial in adolescent subjects with moderate-to-severe AD who received tralokinumab (150 mg or 300 mg) or placebo for up to 52 weeks. This randomised, double-blind trial is the basis for the clinical pharmacology and efficacy evaluation in adolescent subjects with AD and is the primary source of new safety data included in this application.

Supportive trials:

- ECZTEND – an ongoing phase 3 extension trial in subjects with moderate-to-severe AD, including adolescent subjects who completed ECZTRA 6 and who will receive tralokinumab 300 mg Q2W open-label in ECZTEND. As this trial is ongoing, only information on exposure, SAEs, and AEs leading to permanent discontinuation of IMP for the adolescent subjects transferred from ECZTRA 6 is included in this application as additional long-term safety data. The data cut-off for the safety data from ECZTEND is 31-Mar-2021.
- CD-RI-CAT-354-1054 – a completed phase 1 trial in adolescent subjects with asthma who received a single dose of tralokinumab 300 mg. PK profiling from this open-label trial is part of the clinical pharmacology evaluation, and information on AEs is included as supportive safety data.

3.2. Favourable effects

The primary endpoints i.e EASI-75 at week 16 and IGA 0 or 1 at week 16 for both doses investigated in the initial treatment period were met.

In the primary analysis of the primary estimand, the proportion of patients with IGA 0 or 1 at week 16 was higher in both tralokinumab treatment groups (21.4% and 17.5% for 150 mg Q2W group and 300 mg Q2W group, respectively) than in the placebo group (4.3%) with $p<0.001$ for 150 mg Q2W group and 0.002 for 300 mg Q2W group.

Very similar results were observed for sensitivity analysis 1 of the primary estimand.

Also, the proportion of patients with EASI-75 at week 16 was higher in the tralokinumab groups (28.6% and 27.8 % for 150 mg Q2W group and 300 mg Q2W group, respectively) than in the placebo group (6.4%). The observed differences were statistically significant ($p<0.0001$ for each).

For IGA 0/1 and EASI75, the placebo response was lower in ECZTRA 6 than in the adult monotherapy pool, and thus the treatment difference to placebo was slightly higher in adolescents than in adults.

In ECZTRA 6, for IGA 0/1 the estimated difference to placebo was 17.5% (p<0.001) with tralokinumab 150 mg Q2W and 13.8% (p=0.002) with tralokinumab 300 mg Q2W. By comparison, ECZTRA 1+2 for IGA 0/1 the estimated difference to placebo was 9.8 % (p<0.001).

In ECZTRA 6, for EASI-75 the estimated difference to placebo was 22.5 % (p<0.001) with tralokinumab 150 mg Q2W and 22.2% (p<0.001) with tralokinumab 300 mg Q2W. By comparison, ECZTRA 1+2 for EASI-75 the estimated difference to placebo was 16.9 % (p<0.001).

For the initial treatment period the secondary endpoints results support the effects seen in the Primary Endpoints. For secondary endpoints including those under multiplicity adjustment (i.e. a reduction of Adolescent Worst Pruritus NRS of ≥4 from baseline, change SCORAD and CDLQI from baseline to Week 16, for both doses) statistically significantly better results were reported in patients receiving tralokinumab as compared to patients on placebo.

For change in SCORAD, and reduction of Pruritus NRS ≥4 at Week 16, the placebo response was lower in ECZTRA 6 than in the adult monotherapy pool, and thus the treatment difference to placebo was higher in adolescents than in adults. The results from the CDLQI and DLQI questionnaires cannot be directly compared due to differences in the items to be scored, and therefore no conclusion could be made for this endpoint with regard to ECZTRA 6 versus the adult monotherapy pool.

The percentage of responders in the maintenance period in ECZTRA 6 was similar to percentage of responders in the monotherapy pool (ECZTRA 1+2).

In the open-label treatment period the percentage of responders increased overtime. Among the 214 subjects who transferred to open-label treatment at Week 16, 31.3% (95% CI: 25.5 to 37.8) achieved IGA 0/1 at Week 52 and 60.7% (95% CI: 54.1 to 67.0) achieved EASI75 at Week 52.

3.3. Uncertainties and limitations about favourable effects

In the ECZTRA 6 study in the initial treatment period two doses were tested, whereas in the maintenance treatment period four doses were tested i.e 300 mg Q2W, 300 mg Q4W, 150 mg Q2W and 150 mg Q4W. Further, in the open label treatment period patients were receiving tralokinumab 300 mg Q2W with optional use of TCS and/or TCI. Although additional doses were tested in adolescents the applicant is not proposing to alter posology for adolescents as compared to adults.

The applicant justified the dose proposed for adolescents as follows:

-The tralokinumab 150 mg Q2W and 300 mg Q2W dosing regimens tested in ECZTRA 6 showed similar efficacy on the primary and key secondary endpoints however numerically higher responses in the 300 mg Q2W dosing group were recorded for other clinically relevant endpoints such as responder rates for EASI50, reductions in POEM ≥6, CDLQI ≥6 and the reduction in the HADS total score.

-AE of 'dermatitis atopic' (suggesting lack of response) had later onset and the number of such events was lower for tralokinumab 300 mg Q2W as compared to the 150 mg Q2W group

-rescue medications (mainly TCS) were initiated later for tralokinumab 300 mg Q2W as compared to the 150 mg Q2W group

-there was no exposure-related safety concerns (as in the 300 mg Q2W group less TEAEs were reported as compared to the 150 mg Q2W group)

Based on the provided discussion the dose proposed to be used in adolescents is considered as justified.

Although percentage of responders in the maintenance period in ECZTRA 6 was similar to percentage of responders in the monotherapy pool (ECZTRA 1+2) these results should be interpreted with caution due to

the low number of subjects in each treatment group (ranging from 11-14 subjects in the tralokinumab groups) in ECZTRA 6. Further, endpoints in the maintenance period were not included in the multiplicity control strategy.

The posology for adolescents is proposed to be the same as for adults i.e there is an option for every fourth week dosing after 16 weeks of treatment. However, 13 subjects were included in the maintenance period in the 300 mg Q2W arm.

It is noted, that in the open-label treatment period the percentage of responders increased overtime. Among the 214 subjects who transferred to open-label treatment at Week 16, 31.3% (95% CI: 25.5 to 37.8) achieved IGA 0/1 at Week 52 and 60.7% (95% CI: 54.1 to 67.0) achieved EASI75 at Week 52. However, the results in the open-label treatment were confounded by the fact that 50 % of subjects receiving TCSs in this period the applicant discussed these concerns and commented on long-term efficacy in adolescents.

The applicant acknowledged that the long-term efficacy data in adolescents are limited however given that the efficacy and safety profile of tralokinumab 300 mg is overall consistent for the adolescent and adult trial populations, extrapolation of maintenance data from adults to adolescents is warranted. This justification was accepted by the CHMP. It is acknowledged by the CHMP that the long-term study ECZTEND is ongoing and the applicant will provide the CTR in Q4 2022.

There were uncertainties in relation to the use of the product in patients with severe disease at baseline, which required further discussion from the applicant.

In adolescents with severe disease the treatment response was lower as compared to adolescents with moderate disease (IGA 3) however the response which was achieved in adolescents with severe disease was similar to the response observed in adult patients with the same level of disease severity investigated in the pivotal studies supporting the original MAA.

In addition, the response which was achieved in adolescents with severe disease can be considered as clinically relevant. A 1-point reduction on the IGA scale represents a clinically meaningful reduction in disease severity, but a subject with IGA=4 at baseline needed at least a 3-point reduction in IGA to achieve IGA 0/1. Based on the baseline EASI score in subjects with IGA=4 at baseline (mean = 40.4; minimum = 16. a 75% reduction in EASI score in this subgroup was much larger than the 6.6-point reduction identified as the MCID on the EASI scale. This justification provided by the applicant is accepted and it is agreed that the product is also efficacious in patients with severe disease at baseline.

3.4. Unfavourable effects

In ECZTRA 6 study, in the initial treatment period, the incidence of AEs was slightly higher with tralokinumab 150 mg Q2W (67.3%) than with tralokinumab 300 mg Q2W (64.9%) and placebo (61.7%). 9 SAEs were reported in the initial treatment period i.e 1 event in the tralokinumab 300 mg Q2W, 3 in the tralokinumab 150 mg Q2W group and 5 in the placebo group.

The majority of reported AEs were mild. Severe AEs were reported only in 5.1% of subjects in the tralokinumab 150 mg Q2W group, 3.1% of subjects in the tralokinumab 300 mg Q2W groups and 7.4% of subjects in the placebo group. Overall, AE incidences and rates observed during the initial treatment period in ECZTRA 6 were consistent with those seen in the AD pool in adults.

AEs were overall reported at a lower rate for tralokinumab Q2W in the maintenance treatment period compared with tralokinumab Q2W in the initial treatment period. The frequency of AEs varied between the groups with the highest frequency in the placebo group and lowest in the tralokinumab 300 mg Q4W group. No SAEs or deaths were reported in the maintenance treatment period. Except for 1 severe AE reported in the tralokinumab 300 mg Q2W/Q2W group, all AEs were mild or moderate in severity.

67.5% of subject enrolled to the open label treatment period reported AEs. However, the rate of AEs for subjects treated with open-label treatment was lower than the rate of AEs in the initial treatment period (349.4 events per 100 PYE in the open label period versus 441.0 events per 100 PYE with tralokinumab 300 mg Q2W and 596.6 events per 100 PYE with tralokinumab 150 mg Q2W in the initial treatment period).

The majority of AEs reported were mild. Severe AEs were reported in 4 subjects. 7 SAEs were reported in 7 subjects at a rate of 4.63 events per 100 PYE in subjects receiving open-label treatment and the rate was comparable with the rate of SAEs in the initial treatment period. There were 2 AEs that led to permanent discontinuation of IMP.

In general, there was not apparent increase in the frequency of AEs over time and the rate of AEs for subjects treated with open-label treatment was lower than the rate of AEs in the initial treatment period.

In all treatment periods (i.e initial, maintenance and open label), the SOC with the highest incidence and rate of AEs were 'infections and infestations', 'skin and subcutaneous tissue disorders', and 'general disorders and administration site conditions'.

In the initial treatment period viral upper respiratory tract infection, dermatitis atopic, and upper respiratory tract infection were the most frequently reported AEs in all treatment groups.

Viral upper respiratory tract infection, upper respiratory tract infection, injection site reaction, injection site pain, nausea, dyspepsia and headache were reported with the higher frequency and with higher rate as compared to placebo.

The incidence and rate of AEs in the SOC 'psychiatric disorders' were higher in the tralokinumab groups than with placebo however the majority of preferred terms within this SOCs were single events. There was no apparent increase in the incidence and rate of AEs in the SOC of 'eye disorders'.

In general, in the maintenance treatment period and open-label treatment period types of AEs reported were similar to those reported during the initial treatment period. Again, viral upper respiratory tract infection' and 'upper respiratory tract infection' were most frequently reported. There is no apparent increase in the frequency and rate of any type of AEs including injection site reactions.

The distribution patterns of AEs across SOCs and PTs observed in ECZTRA 6 were generally similar to the patterns observed in adults, except for lower incidences and rates in ECZTRA 6 for AEs reported in the SOC 'skin and subcutaneous tissue disorders' (mainly driven by the PT 'dermatitis atopic') and for the PT 'conjunctivitis'.

In general, during the initial treatment period in ECZTRA 6, the frequency and the rate of the related AEs was higher in the tralokinumab groups (26.5% for 150 mg Q2W and 25.8% for 300 mg Q2W) than for the placebo group (21.3%). The incidence and rate of related AEs in the SOC 'general disorders and administration site conditions was the highest.

No deaths were reported during the ECZTRA 6 trial. Overall, SAEs were reported with low frequencies in all treatment groups in the entire trial and no pattern in SOCs or preferred terms was apparent. In total, 19 SAEs were reported: 9 in the initial treatment period (4 in the treatment arms), 7 with open-label treatment, and 3 in the safety follow-up treatment period. All SAEs were moderate or severe, all except for 1 SAE were assessed as not related to IMP by the investigator. 1 subject had a moderate 'gastritis' with hospitalisation 318 days after first and 6 days after latest dose of IMP. The event was considered possibly related to IMP by the investigator but was considered not related to IMP by the sponsor due to the subject's risk factors.

In ECZTRA 6, the following AEs were predefined as AESIs: eczema herpeticum, malignancies diagnosed after randomisation, skin infection requiring systemic treatment and eye disorders (conjunctivitis, keratoconjunctivitis, and keratitis).

In total, 2 AESIs of 'eczema herpeticum (1 in the treatment arm) were reported.

24 AESIs of skin infection requiring systemic treatment were reported in ECZTRA 6. The rate of skin infection requiring systemic treatment in the initial treatment period was higher in the tralokinumab groups (23.86 for 150 mg Q2W and 10.8 for 300 mgQ2W) as compared to the placebo group (7.16).

31 AESIs of 'eye disorders' were reported in the trial. Most of the AESIs of 'eye disorders' were conjunctivitis; only 2 events of keratitis and no events of keratoconjunctivitis were reported. The rate of conjunctivitis was slightly higher in the 150 mg Q2W group than in placebo group. Conjunctivitis is listed in the SmPC. There was no increase in the rate of eye disorders in ECZTRA 6 as compared to the AD pool in adults.

As for the initial safety evaluation of tralokinumab in adults, other safety areas of interest were included in the evaluation of data from ECZTRA 6 based on pre-defined MedDRA search criteria.

No imbalances were observed between ECZTRA 6 and the AD pool in respect of other safety areas of interest such as anaphylaxis and serious allergic reactions, immune complex disease, injection site reactions, severe or serious infections, medication errors, suicidality and psychiatric disorders, rare adverse events, cardiovascular events of interest and malignancy with exception of the incidence of severe infections requiring treatment with oral antibiotics/antivirals/antifungal for more than 2 weeks for which the higher rate was reported in ECZTRA 6 as comparted to the AD pool.

In general, the safety profile of tralokinumab in adolescents was similar to adults. No new major safety issues were identified.

3.5. Uncertainties and limitations about unfavourable effects

No major issues in relation to safety were identified.

Further discussion was required for the following safety concerns: 1 subject in the tralokinumab 150 mg Q2W group had a severe 'cerebrovascular accident' (reported term: 'stroke') with hospitalisation 57 days after first dose of tralokinumab, which unusual finding for an adolescent patient. Cases of stroke and TIA were reported in the adult clinical studies and this issue was discussed during the original MAA. The applicant considers that the occurrence in ECZTRA 6 of a single cardiovascular event with confounding factors does not change the evaluation from the original MAA that treatment with tralokinumab is not associated with a higher risk of cardiovascular events. This is accepted. The applicant was requested to present any further cases of cardiovascular events seen in adolescents in PSUR.

3.6. Effects Table

Table 5 ***Effects Table for Adtralza for the treatment of moderate to severe atopic dermatitis in adult and adolescent patients 12 years and older who are candidates for systemic therapy.***

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
IGA 0/1 at week 16	A score of clear or almost clear on the IGA scale Monotherapy	%	**150mg Q2W** 21/98 (21.4%) **300mg Q2W** 17/97(17.5%) **ECZTRA 1+2** 263/1169 (22.5%)	4/94 (4.3%) **ECZTRA 1+2**	**150mg Q2W** Difference = 17.5% 95% CI= (8.4; 26.6) P-value <0.001 **300 mg Q2W** Difference = 13.8% 95% CI= (5.3; 22.3) P-value =0.002 **ECZTRA 1+2** Difference = 9.8% 95% CI= (6.4; 13.3) P-value <0.001	ECZTRA 6 ECZTRA 1+2

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
EASI-75 at week 16	At least 75% reduction in EASI score Monotherapy	%	**150mg Q2W** 28/98 (28.6%) **300mg Q2W** 27/97(27.8%) **ECZTRA 1+2** 346/1192 (29%)	6/94 (6.4%) **ECZTRA 1+2** 48/398 (12.1%)	**150mg Q2W** Difference = 22.5% 95% CI= (12.4; 32.6) P-value <0.001 **300 mg Q2W** Difference = 22.0% 95% CI= (12.0; 32.0) P-value =<0.001 **ECZTRA 1+2** Difference = 16.9% 95% CI= (12.8; 20.9) P-value <0.001	ECZTRA 6 ECZTRA 1+2
Reduction of Adolescent Worst Pruritus NRS	Reduction of Adolescent Worst Pruritus NRS (weekly average) of at least 4 from baseline to Week 16 Monotherapy	%	**150mg Q2W** 22/95 (23.2%) **300mg Q2W** 24/96(25.0%) **ECZTRA 1+2** 263/1169 (22.5%)	3/90 (3.3%)	**150mg Q2W** Difference = 19.9% 95% CI= (10.6; 29.2) P-value <0.001 **300 mg Q2W** Difference = 21.7% 95% CI= (12.3; 31.1) P-value =<0.001 **ECZTRA 1+2** Difference = 12.6% 95% CI= (8.9; 16.4) P-value <0.001	ECZTRA 6 ECZTRA 1+2
Unfavourable Effects						
AEs over 16 weeks	Patients with ≥1 AE	%	**150mg Q2W** 67.3% **300mg Q2W** 64.9% **ECZTRA 1+2** 65.9%	61.7% **ECZTRA 1+2** 67.4%		ECZTRA 6 ECZTRA 1+2
SAEs over 16 weeks	Patients with ≥1 SAE	%	**150mg Q2W** 3.1% **300mg Q2W** 1% **ECZTRA 1+2** 2.1%	5.3% **ECZTRA 1+2** 2.8%		ECZTRA 6 ECZTRA 1+2
	Serious infections	%	**ECZTRA 6 Q2W Total** 0.5% **ECZTRA 1+2** 0.4%	1.1% **ECZTRA 1+2** 1.1%		ECZTRA 6 ECZTRA 1+2
AESI's over 16 weeks	Viral Upper respiratory tract infections	%	**150mg Q2W** 19.4% **300mg Q2W** 12.4% **ECZTRA 1+2** 15.7%			ECZTRA 6 ECZTRA 1+2
	Eczema herpeticum	%	**ECZTRA 6 Q2W Total** 0.5% **ECZTRA 1+2**	1.1% **ECZTRA**		ECZTRA 6 ECZTRA 1+2

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
			0.3%	**1+2** 1.5%		
	Conjunctivitis	%	**ECZTRA 6 Q2W Total** 3.6% **ECZTRA 1+2** 7.5%	2.1% **ECZTRA 1+2** 3.2%		
	Injection site reactions	%	**150mg Q2W** 6.1% **300mg Q2W** 2.1% **ECZTRA 1+2** 3.5%			

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The primary endpoints of this study were EASI-75 at week 16 and IGA 0 or 1 at week 16. These two primary endpoints were met.

In the primary analysis of the primary estimand, the proportion of patients with IGA 0 or 1 at week 16 was higher in both tralokinumab treatment groups (21.4% and 17.5% for 150 mg Q2W group and 300 mg Q2W group, respectively) than in the placebo group (4.3%) with p<0.001 for 150 mg Q2W group and 0.002 for 300 mg Q2W group.

Very similar results were observed for sensitivity analysis 1 of the primary estimand.

Also, the proportion of patients with EASI-75 at week 16 was higher in the tralokinumab groups (28.6% and 27.8 % for 150 mg Q2W group and 300 mg Q2W group, respectively) than in the placebo group (6.4%). The observed differences were statistically significant (p<0.0001 for each).

In ECZTRA 6, for IGA 0/1 the estimated difference to placebo was 17.5% (p<0.001) with tralokinumab 150 mg Q2W and 13.8% (p=0.002) with tralokinumab 300 mg Q2W. By comparison, ECZTRA 1+2 for IGA 0/1 the estimated difference to placebo was 9.8 % (p<0.001).

In ECZTRA 6, for EASI-75 the estimated difference to placebo was 22.5 % (p<0.001) with tralokinumab 150 mg Q2W and 22.2% (p<0.001) with tralokinumab 300 mg Q2W. By comparison, ECZTRA 1+2 for EASI-5 the estimated difference to placebo was 16.9 % (p<0.001).

The results of other secondary endpoints for the initial treatment period including those under multiplicity adjustments are providing supporting evidence.

In relation to the efficacy results beyond Week 16, they are comparable between adults and adolescents however the strength of evidence is lower as compared to the initial treatment period.

Although percentage of responders in the maintenance period in ECZTRA 6 was similar to percentage of responders in the monotherapy pool (ECZTRA 1+2) these results should be interpreted with caution due to the low number of subjects in each treatment group (ranging from 11-14 subjects in the tralokinumab groups) in ECZTRA 6. Further, endpoints in the maintenance period were not included in the multiplicity

control strategy. The posology for adolescents is proposed to be the same as for adults i.e there is an option for every fourth week dosing after 16 weeks of treatment. However, 13 subjects were included in the maintenance period in the 300 mg W4Q arm.

It is noted, that in the open-label treatment period the percentage of responders increased overtime. Among the 214 subjects who transferred to open-label treatment at Week 16, 31.3% (95% CI: 25.5 to 37.8) achieved IGA 0/1 at Week 52 and 60.7% (95% CI: 54.1 to 67.0) achieved EASI75 at Week 52. However, the results in the open-label treatment were confounded by the fact that 50 % of subjects receiving TCSs in this period.

No major issues in relation to safety were identified.

3.7.2. Balance of benefits and risks

Adtralza is currently approved for the treatment of moderate-to-severe atopic dermatitis in adult patients who are candidates for systemic therapy. The results of the ECZTRA 6 study are considered to provide adequate evidence of efficacy of Adtralza in the treatment of moderate-to-severe atopic dermatitis in adolescent patients 12 years and older who are candidates for systemic therapy. The efficacy results for the initial treatment period are comparable between adults and adolescents.

No major issues in safety were identified and the safety profile of tralokinumab in adolescents was similar to the safety profile in adults.

3.8. Conclusions

The overall B/R of Adtralza for the treatment of moderate-to-severe atopic dermatitis in adolescent patients 12 years and older who are candidates for systemic therapy is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of adolescent patients (12-17 years) for Adtralza based on final study LP0162-1334 (ECZTRA 6): a multicentre, randomised, double-blind, placebo-controlled study in adolescent patients 12 to 17 years of age with moderate-to-severe atopic dermatitis to evaluate the efficacy and safety of tralokinumab monotherapy in this population group. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB are recommended.

Paediatric data

The CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0292/2021 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Adtralza -H-C-005255-II-0002'