22 April 2021
EMA/266138/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Adtralza

International non-proprietary name: tralokinumab

Procedure No. EMEA/H/C/005255/0000

Note

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

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List of abbreviations

2-AB	2-aminobenzamide
ADA	Anti-drug antibody
ADCC	Antibody dependent cell-mediated cytotoxicity
AEX	Anion exchange chromatography
APF	Animal protein free
APFS	Accessorized pre-filled syringe
AUC	Analytical Ultracentrifugation
BBR	Bioburden reduction
BPR	Bubble point ratio
BSA	Bovine serum albumin
CBP	Carboxypeptidase B
CD	Circular dichroism
CDC	Complement dependent cytotoxicity
CDR	Complementarity-determining region
CDR	Complementarity determining regions
CEX	Cation exchange chromatography
CFU	Colony forming units
CI	Confidence intervals
cIEF	Capillary isoelectric focusing
CPP	Critical process parameter
CQA	Critical Quality Attribute
CQA	Critical quality attribute
CV	Column volume
CWL	Cool white light
dFBS	dialyzed foetal bovine serum
Dip	Diptheria
DMB	1, 2-diamino-4, 5-methylenoxybenzene
DO	Dissolved oxygen
DS	Drug Substance
DSC	Differential scanning calorimetry
ELISA	Enzyme-linked immunosorbent assay
EOPCB	End-of-production cell bank

Fab	Fragment antigen-binding
FDA	Food and Drug Administration
FMEA	Failure Mode and Effects Analysis
FTIR	Fourier transform infrared spectroscopy
GMP	Good Manufacturing practices
GSD	Geometric standard deviation
HC	Heavy chain
HCDNA	Host cell DNA
HCP	Host cell protein
HEK	Human embryonic kidney
Hib	Haemophilus influenza type b
HILIC	Hydrophilic interaction chromatography
HPC	High positive control
HPLC	High performance liquid chromatography
HP-SEC	High-performance size exclusion chromatography
HUVEC	Human umbilical vein endothelial cell
IEC	Ion exchange chromatography
IPC	In-process control
ISF	Impurity safety factor
KD	Dissociation constant
KPPs	Key process parameters
LC	Light chain
LC	Liquid chromatography
LIVCA	A limit-of-in-vitro-cell-age
LPC	Low positive control
LRV	Log value reduction
MALS	Multiangle Light Scattering
MC	Microbial control
MCB	Master cell bank
MIA	Manufacturer's Authorisation
MPC	Medium positive control
MS	Mass spectrometry
MSD	MesoScale Discovery
MVM	Minute Virus of Mice

NAb	Neutralising antibody
NANA	N-acetylneuraminic acid
NC	Negative control
NCPP	Non-Critical process parameter
NF	Normalisation factor
NGNA	N-glycolylneuraminic acid
NKPPs	Non-key process parameters
NOAEL	No observed adverse effect level
NRGE	Non-reduced gel electrophoresis
NWP	Normalised water permeability
OOS	Out of specification
OQ	Operational Qualification
PA	Performance attribute
PDL	Population doubling limit
PFS-SA	Prefilled syringe subassembly
PNGase	F Peptide-N-glycanase
PPQ	Process performance qualification
PQ	Performance Qualification
PRS	Primary reference standard
PRV	Pseudorabies Virus
PS80	Polysorbate 80
PTMs	Post-translational modifications
PV	Process validation
QP	Qualified person
Q-TOF	Quadrupole time-of-flight
RGE	Reduced gel electrophoresis
RLPs	Retrovirus-like particles
RP-HPLC	Reverse phase HPLC
RPN	Risk priority number
RT	Reverse transcriptase
scFv	Single chain fragment variable
SEAP	Secreted embryonic alkaline phosphatase
SEC	Size exclusion chromatography
SPR	Surface plasmon resonance

SST	System Suitability Test
sTAG	Sulfo-tagged
SVPs	Sub visible particles
TEM	Transmission electron microscopy
Tet	tetanus
TSE/BSE	Transmissible Spongiform Encephalopathies/Bovine Spongiform Encephalopathy
TTC	Threshold of toxicological concern
UF/DF	Ultrafiltration/diafiltration
UHPC	Ultra-high positive control
UPB	Unprocessed bulk
UV	Ultraviolet
VCAM-1	Vascular cell adhesion molecule-1
VCD	Viable cell density
VF	Virus filtration
WCB	Working cell bank
WFI	Water for injection
WRS	Working reference standard
XMuLV	Xenotropic Murine Leukaemia Virus

1. Background information on the procedure

1.1. Submission of the dossier

The applicant LEO Pharma A/S submitted on 27 April 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Adtralza, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

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

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0145/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0145/2020 was not yet completed as some measures were deferred

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant 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.

New active Substance status

The applicant requested the active substance tralokinumab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
15 September 2016	EMEA/H/SA/2714/2/2016/II	Dr Jan Mueller-Berghaus and Dr Peter Kiely

The Scientific advice pertained to the following clinical aspects:

- Agreement on the phase 3 program comprising 2 pivotal studies and a long-term extension (LTE) study in terms of population, endpoints, study design and statistical analysis plan;
- Dose and dose regimen selection for pivotal studies and associated posology recommendations for induction and maintenance phase;
- Managing AD medication during phase 3 studies (i.e. as prohibited, permitted concomitant, permitted rescue) and handling of patients on rescue or prohibited treatments in the statistical analyses;
- Primary and secondary endpoints;
- Hypothesis testing formulation to avoid multiplicity issues;
- Strategy regarding development of a predictive biomarker;
- Safety database;
- Strategy to commence self-administration testing in the LTE study and adequacy of the data to support self-administration claim at MAA.

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: Johann Lodewijk Hillege

The application was received by the EMA on	27 April 2020
The procedure started on	21 May 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	10 August 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	10 August 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	19 August 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	17 September 2020
The applicant submitted the responses to the CHMP consolidated List of	18 December 2020

Questions on	
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	01 February 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 February 2021
The CHMP agreed on a list of outstanding issues <in writing and/or in an oral explanation> to be sent to the applicant on	25 February 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	21 March 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	07 April 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Adtralza on	22 April 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Atopic dermatitis (AD) is a chronic or chronically relapsing inflammatory skin disease. It is characterised by eczematous lesions including erythema, excoriations, lichenification, infiltration, oozing, xerosis and pruritus.

All of 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.

2.1.2. Epidemiology

AD is the most common inflammatory skin disease in the developed world. The onset of disease is usually reported in childhood, but the prevalence in adults remains high despite some tendency to remission. Approximately 1 in 4 adults reports onset of disease in adulthood[1].

The prevalence varies between regions: in a web-based survey (2018) using a modified UK Working Party definition of AD, the 1-year prevalence of AD in adults was reported to be 4.3% in Japan, 8.1% in Canada, 9.4% in Europe, and 11.9% in the US[2]. In a similar web-based survey (2018) that used data from the US Census Bureau to create adjusted sample weights, the 1-year prevalence of AD representative for the adult US population was estimated to be 7.3%[3].

2.1.3. 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 human type 2 helper (Th2) lymphocytes that can be found in abundance in AD skin lesions together with increased levels of Th2-derived cytokines, especially interleukin-13 (IL-13). The action of IL-13 on its target cells results in epidermal barrier disruption, allergen reactivity and inflammation which drive the pathogenesis of AD.

[1] Lee HH, Patel KR, Singam V, Rastogi S, Silverberg JI. A systematic review and meta-analysis of the prevalence and phenotype of adult-onset atopic dermatitis. J Am Acad Dermatol. 2019 Jun;80(6):1526-1532.e7.
[2] Barbarot S, Auziere S, Gadkari A, Girolomoni G, Puig L, Simpson EL, Margolis DJ, de Bruin-Weller M, Eckert L. Epidemiology of atopic dermatitis in adults: Results from an international survey. Allergy. 2018;73(6):1284-1293.
[3] Silverberg JI, Gelfand JM, Margolis DJ, Boguniewicz M, Fonacier L, Grayson MH, Simpson EL, Ong PY, Chiesa Fuxench ZC. Patient burden and quality of life in atopic dermatitis in US adults: A population-based cross-sectional study. Ann Allergy Asthma Immunol. 2018;121(3):340-347.

2.1.4. Clinical presentation, diagnosis

AD is a chronic or chronically relapsing inflammatory skin disease characterised by pruritus, xerosis, and eczematous lesions. Especially pruritus and skin infections which are a major complication in AD compromise health and lower the quality of life and, in the worst case, can result in psychic comorbidities as anxiety and depression.

The diagnosis of AD is made clinically as there is currently no reliable biomarker that can distinguish the disease from other entities. The clinical diagnosis is based on historical features, morphology and distribution of skin lesions, and associated clinical signs. Formal sets of criteria have been developed by various groups to aid classification[4].

2.1.5. Management

Management of moderate-to-severe AD is challenging because of the chronicity of the disease and the limited therapeutic options that are both efficacious and have an acceptable long-term safety profile. A "control-based" and "risk-based" model of disease management, in which an initial diagnosis is followed by treatment according to categorisation of severity, is usually recommended. The pharmacological treatment algorithm for AD progresses from mild topical anti-inflammatory therapy, to high potency topical therapy, and in some cases leads to systemic immunomodulatory therapy. In general, the key treatment guidelines recommend the use of systemic treatment in patients that are not adequately controlled by optimised topical therapies[4,5,6,7,8].

Current therapies and interventions include education, emollients, and avoidance of exacerbating factors. For induction and intermittent topical corticosteroids therapy (TCS), topical calcineurins (TCI) and topical phosphodiesterase 4 (PDE4) inhibitors are used. The topical therapies can be cumbersome and for TCS and TCI associated with side effects that can limit their use. Phototherapy (PUVA, UV-B, narrow band UV-B, UV-A and UV-A1) is used for widespread disease but can be time consuming and long-term use can be associated with side effects. Systemic oral therapies (azathioprine, methotrexate, mycophenolate mofetil and ciclosporin) are used for severe and recalcitrant disease but they can be associated with toxicities that can limit their use.

Currently, 2 systemic therapies are centrally approved in the EU for patients with AD: dupilumab (Dupixent), an injectable monoclonal antibody against IL4/IL13 approved in 2017 for moderate-to-severe AD in adults and adolescents 12 years and older who are candidates for systemic therapy; and baricitinib (Olumiant), a Janus kinase (JAK)-inhibitor approved in July 2020 for moderate to severe AD in adult patients who are candidates for systemic therapy. In addition, two topical treatments (ointments) are approved in AD in the European Union (EU): crisaborole (Staquis) a PDE-4 inhibitor and tracrolimus monohydrate (Protopic) a calcineurin inhibitor.

[4] Eichenfield LF, Tom WL, Chamlin SL, Feldman SR, Hanifin JM, Simpson EL, Berger TG, Bergman JN, Cohen DE, Cooper KD, et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. J Am Acad Dermatol. 2014;70(2):338-351.
[5] Wollenberg A, Barbarot S, Bieber T, Christen-Zaech S, Deleuran M, Fink-Wagner A, Gieler U, Girolomoni G, Lau S, Muraro A, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I. J Eur Acad Dermatol Venereol. 2018;32(5):657-682.
[6] Wollenberg A, Barbarot S, Bieber T, Christen-Zaech S, Deleuran M, Fink-Wagner A, Gieler U, Girolomoni G, Lau S, Muraro A, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part II. J Eur Acad Dermatol Venereol. 2018;32(6):850-878.
[7] Sidbury R, Davis DM, Cohen DE, Cordoro KM, Berger TG, Bergman JN, Chamlin SL, Cooper KD, Feldman SR, Hanifin JM, et al. Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. J Am Acad Dermatol. 2014;71(2):327-349.
[8] Katoh N, Ohya Y, Ikeda M, Ebihara T, Katayama I, Saeki H, Shimojo N, Tanaka A, Nakahara T, Nagao M, et al. Clinical practice guidelines for the management of atopic dermatitis 2018. J Dermatol. 2019;46(12):1053-1101.

About the product

Tralokinumab is a fully human immunoglobulin G4 (IgG4) monoclonal antibody that binds to IL-13 at an epitope that overlaps with the binding site of the IL-13Rα receptors, preventing IL-13 from binding to both IL-13Rα1 and IL-13Rα2.

Tralokinumab belongs to the pharmacological class of immunomodulators, interleukin inhibitors.

The proposed indication for tralokinumab is "for the treatment of moderate-to-severe atopic dermatitis in adult patients who are candidates for systemic therapy". The summary of product characteristic (SmPC) also states that tralokinumab could be used with or without TCS or TCI.

The proposed strength and pharmaceutical form are a 150 mg solution for injection in pre-filled syringe. Tralokinumab is intended to be administered by subcutaneous (SC) injection into the thigh or abdomen.

Type of Application and aspects on development

The application was submitted under the legal basis 8(3) of Directive 2001/83/EC which corresponds to a complete and independent application.

The applicant requested an EMA scientific advice for tralokinumab for the treatment of AD. The questions concerned the clinical development (see in section 1.1. 'Scientific advice').

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a solution for injection containing 150 mg of tralokinumab active substance in 1 mL. Other ingredients are sodium acetate, acetic acid, sodium chloride, and Polysorbate 80. The product is available in a siliconised type-1 clear glass pre-filled syringe with 27gauge ½ inch thin wall stainless steel staked needle, elastomer plunger stopper, extended finger flange and needle guard (presentations of 2 prefilled syringes, multipack containing 4 (2 packs of 2) pre-filled syringes and multipack containing 12 (6 packs of 2) pre-filled syringes).

2.2.2. Active Substance

General Information

The active substance (drug substance, DS) is tralokinumab, a human IgG4λ monoclonal antibody that specifically binds to human interleukin 13 (IL-13), blocking interactions with the IL-13 receptor. It is manufactured in a n NS0 murine cell line. The antibody is composed of two identical heavy chains of 49,413 Da each, and two identical light chains of 22,664 Da each. Tralokinumab has an N-linked oligosaccharide attachment site in the Fc region at residue Asn-299 and has a relative molecular mass of approximately 147 kDa (including oligosaccharides).

Manufacture, process controls and characterisation

Description of manufacturing process and process controls

The active substance is manufactured at AstraZeneca Pharmaceuticals LP Frederick Manufacturing Centre (FMC), Maryland, USA. The documentation provided supports that the DS is manufactured and tested in a GMP environment.

The tralokinumab DS manufacturing process is initiated by thawing and inoculating cells from the characterised NS0 working cell bank (WCB) vial into culture medium. The inoculum expansion process is carried out using multiple steps until sufficient cells to seed the production bioreactor are reached. The production bioreactor is operated in fed batch mode. Harvest of the production bioreactor is initiated within the specified step duration.

Downstream manufacture comprises processing by chromatography steps, viral inactivation and removal steps, concentration and buffer exchange, and formulation. The final DS is filtered into bags and stored.

Process parameters and In-Process Controls (IPCs) are listed for the manufacturing process. IPCs are in place to control for microbial contamination and have associated action limits.

Two purification process steps are qualified as reprocessing steps for the manufacture of the active sub-stance: virus refiltration and formulated bulk refiltration. Procedures with criteria for each reprocessing step have been adequately described.

Control of materials

The applicant has provided a list of raw materials used in DS manufacture including where in the process they are used as well as names of suppliers. Specifications are provided for the non-compendial raw materials. The active substance is expressed in an NS0 cell line. The development of the Master Cell Bank (MCB) and WCB are sufficiently described. The cell banks were characterised according to ICH requirements Q5A (R1), Q5B and Q5D. A protocol has been presented for preparation and qualification of future working cell banks.

It is acknowledged that NS0 cell lines, which are used to manufacture many EU approved biologics, are known to harbour endogenous retroviruses. As discussed further in the adventitious agents section, viral clearance data presented supports the conclusion that the presence of specific endogenous retroviruses in the cell banks used for the production of tralokinumab presents negligible safety risk to patients.

Control of critical steps and intermediates

The approach for process characterisation is stepwise, as follows: verification of suitability of scale-down model, risk assessment to define characterisation study design, execution of process characterisation studies, and finally determination of Critical Process Parameters (CPPs).

The scaled down models are considered representative of commercial scale.

Process characterisation was conducted on each unit operation. For each unit operation the risk assessment rationale for parameters that were not subject to further characterisation studies is also provided. For those process parameters assessed as having an impact on critical quality attributes (CQAs), the ranges of that process parameter were studied to determine an impact on the relevant CQAs.

Overall, the proposed control strategy, which is based on extensive product and process understanding from manufacturing experience, comparability/process characterisation and process validation data, is considered appropriate to ensure process consistency and results in a product capable of meeting the required quality attributes.

Process validation

Manufacture of tralokinumab DS at the commercial-scale facility at AstraZeneca Pharmaceuticals LP Frederick, USA has been validated using a stepwise approach including process design, process validation and continued process verification. The process validation included CPPs, Non-Critical Process Parameters (NCPPs), IPCs, Microbial Controls (MCs), and Performance Attributes (PAs). Full DS process validation was performed on the process validation lots. All proposed commercial release specifications were met for the validation lots.

DS shipping qualification studies were performed to support shipping of tralokinumab DS to the finished product fill location. The results of the operational qualification and performance qualification support suitable qualification.

Manufacturing process development

A systematic severity assessment for identification of CQAs was conducted. The criticality of an attribute directly relates to the biological activity, pharmacokinetics/pharmacodynamics, safety and immunogenicity of the product and the severity is based on both impact and uncertainty of the attribute. The assigned CQAs are acceptable.

Seven different manufacturing processes were used during the development of tralokinumab. The development began in 2003 with Process 1. Between 2004 and 2012, five additional processes were introduced. None of the Process 1 to 6 batches were used in clinical studies for the intended atopic dermatitis indication. In 2013 Process 7 was introduced, with two further Process 7 campaigns in 2016 and 2018. The 2013 Process 7 batches were used in the pivotal Phase 2b/3 atopic dermatitis studies which enrolled over 1500 subjects. The 2016 Process 7 batches were also used in these three pivotal studies and in a further three Phase 3 clinical studies in atopic dermatitis (ECZTRA 4, 5 and 6), and in the ECZTEND open label extension study (1125 subjects). The 2018 Process 7 batch was also used in the ECZTEND study. Three Process 7 process validation batches were also manufactured in 2018.

Process changes across these seven processes include scale up, site changes (new production facilities), changes to media and nutrient feed formulations, new WCB, changes to purification steps and, formulation development, amongst other minor changes. Detailed tables of lot genealogy of all material manufactured from Process 1 through Process 7 that were used in nonclinical and clinical studies are provided.

Studies on the impact of process changes on viral clearance are provided. It can be acknowledged that none of the process changes have negatively impacted viral safety of the finished product. Detailed comparability testing performed to support product quality throughout the product development is presented, and based on the extensive data presented for all processes the claim of comparability is supported. The results are within their established acceptance criteria and aligned with process manufacturing trends.

Overall, the data presented supports the comparability of material used in the pivotal studies and PPQ batches.

Characterisation

Tralokinumab has been comprehensively characterized for primary structure, secondary structure, charge heterogeneity, size heterogeneity, and biological activity.

Molecular weight was determined and the primary sequence was confirmed. There was 100% coverage of the light chain and heavy chain. The N-linked oligosaccharide profile was analysed.

The charge profile of tralokinumab is influenced by deamidation, glycation, sialylation, half antibody, oxidation, aglycosylation, and succinimide.

Size heterogeneity was characterized by several analytical methods. The level of aggregates was low.

Higher order structure was examined. The secondary and tertiary structure was typical for a mAb.

Biological activity was characterized using an IL-13 reporter gene assay and a HUVEC-based enzyme-linked immunosorbent assay (ELISA). Tralokinumab shows a dose-dependent inhibition of IL-13 in both assays. IL-13 binding was also measured. As IL-13 is a soluble target, tralokinumab is not considered to have effector function. Therefore, Antibody-mediated cytotoxicity (ADCC) and Complement-Dependent Cytotoxicity (CDC) were not examined. Binding to the Fc receptors FcγRI, FcγRIIa, FcγRIIb, FcγRIIIa-158V/F, and FcRn were measured by SPR.

Overall, the active substance has been sufficiently characterized.

Impurities

Product- and process-related impurities have been suitably characterised and are considered adequately controlled.

Specification, analytical procedures, reference standards, batch analysis, and container closure

The proposed panel of release tests cover appearance, identity, quantity, purity/impurities, potency, general tests and microbial assurance. In general, the panel of tests is in line with ICH Q6B and Ph. Eur. 2031 *monoclonal antibodies for human* use and is considered appropriate for routine control of a monoclonal antibody both at release and shelf life.

The statistical model used has been adequately described and justified and is considered an acceptable approach for justifying the specifications. Nonetheless, the Applicant is recommended to re-evaluate the active substance and finished product specification limits once 30 batches have been analysed, and to provide these revised specification limits upon availability (see "Recommendations for future quality development").

Analytical methods

The analytical method descriptions for the non-compendial methods are provided in the dossier. The analytical method descriptions include details of reagents, sample preparation, operating conditions, and system suitability tests (SSTs). In general, the method descriptions are considered acceptable.

The in-house methods were validated for accuracy, repeatability, intermediate precision, linearity, range and specificity Overall, the methods have been validated in line with ICH Q2 and are considered appropriate for release testing of the active substance. Compendial analytical procedures were verified and confirmed suitable for their intended use according to the current Ph. Eur. requirements.

Batch analyses

Batch release data has been provided for multiple batches. This includes batches from process 1 to process 7 and covering also batches used in clinical studies. Some of the analytical methods have changed during product development, however historical method changes prior to the introduction of process 7 are not of concern. The data show that the commercial process in capable of producing active substance of consistent quality.

Reference materials

A standard two-tier reference standard system is used with a primary and secondary reference standard. The reference standards have been sufficiently characterized, including release tests and additional characterization tests . A protocol for the qualification of future reference standards has been provided.

Container closure system

The active substance is stored in bags. The bags comply with Ph. Eur. 3.1.7 and Ph. Eur. 5.2.8. Results from extractable and leachables studies have been provided and are considered acceptable.

Stability

Stability studies were generally performed in accordance with ICH Q5C. Data are provided for lots manufactured according to process 7, including the PPQ batches. The quality of these batches is considered representative for the quality of the material used in clinical studies and of the quality of commercial material. The material of construction for the container/closure system used for stability studies is identical to that of the commercial scale container closure.

Real time stability data is provided to support the proposed shelf life.

No significant changes are observed during long term storage. All batches remained within specification over the course of the stability studies.

The applicant proposes a combination of two storage conditions. There is nothing in the stability dataset that would lead to a concern of an out of specification result using this combination storage approach. Therefore, the proposal can be endorsed.

Accelerated and stress stability data was provided. The accelerated and stress stability data confirm the stability-indicating methods

In conclusion, the proposed DS shelf life is deemed justified.

2.2.3. Finished Medicinal Product

The finished product (drug product, DP) is a sterile, preservative-free, solution for subcutaneous (SC) injection presented in a single-dose accessorized pre-filled syringe (APFS). In brief, the PFS is accessorized with a needle safety guard, extended finger flange and plunger rod. The label claim for each APFS is 150 mg tralokinumab in 1 mL. All excipients (sodium acetate trihydrate, glacial acetic acid, sodium chloride, polysorbate 80) are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients or excipients of human / animal origin used in the finished product formulation.

The applied overfill is acceptable and will ensure a dose of 1 mL can be delivered. The DP does not contain an overage of the active pharmaceutical ingredient.

Pharmaceutical development

The goal of formulation development was to achieve a liquid dosage form with sufficient stability at the intended storage condition for long-term storage. The chosen formulation adequately accommodates the active substance's physicochemical properties in terms of stability, solubility and route of administration. This is supported by formulation development studies, stability data and product osmolality.

The intended commercial formulation is the same as that used during clinical studies. There have been changes in the container closure (from vial to APFS) and subsequent changes to the APFS manufacturing process. There have also been site transfers. Comparability is well demonstrated and included data from release testing, characterisation data and data from samples stored under accelerated and stressed conditions.

Container closure

The container closure is a 1 mL long siliconized clear and colorless glass syringe barrel with a 27-gauge, ½-in, special thin-wall staked stainless steel needle, and rigid needle shield. The proposed primary closure is a coated plunger stopper. The glass barrel used complies with Ph. Eur. 3.2.1 (Glass Containers For Pharmaceutical Use), the stopper and shield comply with Ph. Eur. 3.2.9 (Rubber Closures For Containers For Aqueous Parenteral Preparations) and this is endorsed. Given that there is no relevant Ph. Eur. monograph for the steel needle, it is acceptable that it has been detailed to comply with ISO 9626 (stainless steel needle tubing for manufacture of medical devices). Adequate detail, in line with EMA/CHMP/CVMP/QWP/850374/2015 is provided on how the components are sterilised.

The medicinal product includes components which are classified as medical devices. The device is shown to be suitable in relation to the clinical performance of the product (dosing accuracy). Tralokinumab APFS complies with the relevant essential requirements related to the device constituent part according to Annex I of the MDD.

In conclusion, the container closure system is suitable for use based on development studies, stability studies and the fact that it has been developed in accordance with relevant ISO standards, Ph. Eur. texts and EU guidelines.

Process Characterisation

The process and steps included are suitable for the manufacture of this product as demonstrated through process characterisation studies. In brief, the effects of PPs on QAs for each step were characterised. PPs were deemed non-critical if during these studies, no effect on QAs were seen. However, in some instances, some PPs were deemed critical as a precaution. This approach is endorsed.

Manufacture of the product and process controls

Batch release is proposed to be performed at LEO Pharma A/S, Ballerup, Denmark.

The manufacturing process is standard for therapeutic monoclonal antibodies and has been adequately described. The DS is thawed and shipped to the fill facility. At the filling facility, the DS undergoes warming, pooling and mixing, bioburden reduction filtration, temperature equilibration and sterile filtration. Next the syringe is filled and stoppered and undergoes 100% visual inspection. The filled and stoppered syringe is stored until the start of the labelling, assembly, and packaging process. Each individual syringe has a plunger rod inserted. Printed labels are applied to the syringe. Finger flange is assembled together with the safety device (needle safety guard) and merged with the syringe to complete the assembly of the APFS. The APFS is packed with package insert into cartons.

Process controls are deemed adequate. Process parameters and in-process controls are adequately set to control the process leading to consistent quality as demonstrated by PPQ lot data. The proposed process ranges are based on process characterisation data where it is deemed the QAs evaluated as outputs for each step are appropriate. The data provided in support of the ranges is acceptable.

Process validation was performed on three consecutive process validation lots. The data provided demonstrates that the DP manufacturing process is valid and under control for the manufacture of batches of the proposed batch size. The process is capable of producing material of consistent quality.

Product specification, analytical procedures, batch analysis

The finished product specification is considered comprehensive and therefore acceptable. Parameters tested include appearance, quantity, identity, purity/impurities, potency, adventitious agents and general tests.

Data was provided demonstrating that polysorbate-80 (PS-80) remains within specification throughout the DP manufacturing process and during long term and in-use stability. It was therefore deemed acceptable to not include a control for PS-80 at DP release.

Justification of DP acceptance criteria for many tests has been provided in the DS section of the dossier. This is acceptable. Where differences in DS and DP acceptance criteria exist, adequate justification has been provided. As outlined in the active substance section, the Applicant is recommended to re-evaluate the active substance and finished product specification limits once 30 batches have been analysed, and to provide these revised specification limits upon availability (see "Recommendations for future quality development").

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product was requested in the form of a major objection. Based on the information provided in response, it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary. The major objection is considered satisfactorily resolved.

Analytical methods

For the most part, the proposed methods are those included in the DS section of the dossier, which is considered suitable as the DP is the same as the DS, in terms of formulation, and the DP manufacturing process would not be considered to impact on the performance of these tests or on their validation status. Additional testing using Ph. Eur. methods is proposed, which is acceptable. For additional DP specific testing the methods are deemed suitable.

For methods common to both testing DS and DP, no additional validation is performed. This is acceptable. For Ph. Eur. methods specific to DP testing product specific qualification is performed, demonstrating that tralokinumab does not interfere with method performance. DP specific methods have been suitably validated. Method transfer to the proposed QC sites is adequately shown.

Batch analysis

Batch analysis data of all vial (process 1-7) and prefilled syringe lots (process 7) manufactured to date have been provided. All test results complied with the specifications set at the time the batches were tested. The batch analysis results confirm consistency and uniformity of the product and indicate that the process is under control.

Reference materials

The same reference standard is used for release testing of both DS and DP. Given that the methods are the same and the formulation is unchanged from DS to DP, this is acceptable. For details, please refer to the active substance section.

Stability of the product

The claimed shelf life is 36 months at 5°C with an in-use shelf life of 14 days at up to 30°C. Studies in support of this claim are conducted in accordance with ICH guidance. Material is stored in the proposed commercial container and stability indicating attributes have been appropriately identified using temperature stressed conditions.

In support of the proposed shelf life, real-time data at 5°C is provided for several lots. With some minor exceptions the real time data do not reveal any clear trends, even after long term storage. During the claimed shelf life (3 years) no evident changes in any of the parameters are observed.

Data provided in support of the proposed 14 day in-use shelf life at up to 30°C is provided and shows all quality attributes meet their criteria.

Photostability has been appropriately evaluated in accordance with ICH Q1B. The product was shown to be light sensitive. The secondary packaging offers adequate protection against light degradation and the product information instructs the user to store the product in the secondary packaging. This is acceptable.

Data from ongoing extractables and leachables studies is acceptable and show all identified compounds to be below the daily threshold of toxicological concern (TTC).

The stability data provided confirm the proposed shelf life (3 years at 5 °C) and in-use period (room temperature up to 25 °C for a maximum of 14 days).

Adventitious agents

Animal Spongiform Encephalopathy (TSE/BSE)

Materials of animal origin used in host cell line culture, cell line development, cell banking, and the manufacturing process have been described. Certificates of analysis (CoAs), certificates of origin and TSE Certificates of Suitability were provided as relevant.

As required, a risk assessment of the transmission of BSE from materials of animal origin used in the culture and banking of the host cell line has been performed and concludes that the risk posed for potential BSE infectious agent introduction is low.

Viral safety

The programme of testing for the MCB and WCB for virus contamination is adequately described. No infectious viral agents were detected with the exception of endogenous infectious retrovirus. It is acknowledged that some murine cell lines used for the production of monoclonal antibodies will contain endogenous retroviruses (as per ICH Q5A), and it is agreed that the viral clearance data shows the process is sufficiently capable of removing the virus. The applicant provided a risk assessment specifically focused on any potential impact on product safety. The risk assessment presented is considered supportive and it is agreed that the viral clearance data presented (discussed below) supports the conclusion that the presence of endogenous retrovirus in the cell banks used for the production of tralokinumab presents minimal safety risk to patients.

The viral clearance capability of the tralokinumab downstream purification process was evaluated at small scale using four model viruses with different physicochemical properties. Five steps of the purification process were evaluated. For the chromatography steps, both new and used resin was tested and the lowest observed log reduction value (LRV) is claimed for each model virus. Additionally, virus carryover experiments were performed for both the new and used resins to determine the effectiveness of column sanitisation. The results of these studies were found to be supportive of the sanitisation process of each column.

The viral clearance experiments were carried out in accordance with the ICH Q5A and demonstrated that the purification process provides satisfactory cumulative $\log_{10}$ reduction values (LRVs) of the model viruses.

A safety margin was calculated for clearance of endogenous retrovirus-like particles using the defined process clearance data in conjunction with worst case retrovirus-like particle titer results and process

performance data. This is consistent with other approved antibody products manufactured by similar processes.

The overall viral safety of tralokinumab is considered acceptable.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

In response to a major objection raised, the applicant has provided an adequate risk evaluation concerning the presence of nitrosamine impurities which concludes that there is no risk identified. The major objection is therefore considered resolved.

Two recommendations to re-evaluate the active substance and finished product specification have been agreed with the applicant.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

To re-evaluate the active substance specification limits once 30 batches of the active substance have been analysed, and to provide these revised specification limits upon availability.

To re-evaluate the finished product specification limits once 30 batches of the finished product have been analysed, and to provide these revised specification limits upon availability.

2.3. Non-clinical aspects

2.3.1. Introduction

The marketing authorisation application (MAA) comprised a comprehensive battery of pharmacology, pharmacokinetics (PK) and toxicology tests.

The tralokinumab non-clinical pharmacology program evaluated the pharmacodynamics (PD) of tralokinumab in a variety of *in vitro* assays and *in vivo* models (mouse, cynomolgus monkey), as well as any effects of tralokinumab on safety pharmacology endpoints in repeat-dose toxicology studies in the cynomolgus monkey. One single dose PK study of tralokinumab was performed in *Ascaris suum* sensitised cynomolgus monkeys (study CAT354Rp034). Repeat dose toxicokinetics of tralokinumab was assessed from toxicology studies.

The cynomolgus monkey was used in the pharmacology, PK and toxicology studies to support the clinical program because tralokinumab was shown to be pharmacologically active in human and cynomolgus monkey, as it neutralises both human and cynomolgus monkey IL-13. However, tralokinumab did not neutralise the effects of mouse IL-13.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Primary pharmacology in vitro

In initial *in vitro* experiments the binding efficacy of tralokinumab to human recombinant IL-13 was assessed using Biacore analysis and initially determined to be 165 pM, a value that was subsequently adjusted to 58 pM based on further experiment using a more sensitive Biacore instrument. The binding of tralokinumab to IL-13 was demonstrated to prevent the interaction of IL-13 with both of its receptors, IL13Rα1 and IL-13Rα2. Downstream of this IL-13 mediated cell proliferation was significantly antagonised by tralokinumab with proliferation of the IL-13 dependent TF-1 cell line (a human erythroleukemic cell line) inhibited with an IC_{50} of 1.1 nM. Similar effects were seen in HDLM-2 cells (Hodgkin's lymphoma derived cell line) demonstrating the functional consequences of this binding of tralokinumab to IL-13.

In order to investigate the potential modulation of signalling events associated with AD, several *in vitro* studies using human epidermal keratinocytes and dermal fibroblasts were performed. IL-13-induced expression of the inflammatory mediators chemokine ligand 2 (CCL2), chemokine ligand 26 (CCL26), neurotrophic tyrosine kinase receptor type 1 (NTRK1) and IL13RA2 in keratinocytes, and CCL2, CCL11 and POSTN (periostin) in fibroblasts, which have been linked to the pathogenesis of AD, was reduced in a dose dependent manner by tralokinumab treatment. Similarly, the IL-13-mediated reduction in Filaggrin (FLG), FLG2, loricrin (LOR), ELOVL3 and DEFB4A, all genes involved in maintenance of the skin barrier, was significantly attenuated by tralokinumab treatment in differentiated keratinocytes. Importantly, the effects seen on the inflammatory and skin barrier markers were only evident when IL-13 was used as the stimulant and not IL-4, suggesting the specificity of tralokinumab for modulating IL-13 mediated signalling events. In addition, a series of further *in vitro* studies have been performed using assays and endpoints which are more relevant to tralokinumab and its potential to modulate events in the lung and respiratory airways including release of eotaxin-1 from lung fibroblasts and the modulation of eosinophil shape and calcium signalling in bronchial smooth muscle cells. Although these studies are not directly relevant for the proposed indication, they nevertheless provide evidence that inhibition of IL-13 signalling can functionally affect a number of aspects associated with its pro-inflammatory effects. In particular, tralokinumab was seen to significantly reduce the switch of B cells to produce IgE antibodies.

To investigate the ability of tralokinumab to cross reactive with IL-13 from other species, amino acid sequence homology comparisons were performed. A high degree of sequence similarity with IL-13 of 95% was seen between human and cynomolgus monkey. In contrast, the sequence similarity for rodent IL-13 is lower at 55% for mouse IL-13 and 62% for rat IL-13. Based on the lack of activity of tralokinumab in an assay measuring cell proliferation induced by mouse IL-13, it has been concluded that tralokinumab does not bind to rodent IL-13. Tralokinumab was shown to inhibit human and monkey IL-13 mediated TF-1 cell proliferation with comparable potency (IC_{50}=1.1 nM and 1.7 nM, respectively). Affinity binding experiments using surface plasmon resonance binds to recombinant cynomolgus monkey IL-13 with a measured K_D of 0.6 nM, compared to 0.06 nM for human IL-13. Homology analysis of the amino acid residues in the tralokinumab binding epitope between human IL-

13 and cynomolgus monkey IL-13 revealed only one conservative change: Leu100Val. Overall, this data suggest that tralokinumab binds to monkey IL-13 with a comparable affinity to that of human IL-13.

Primary pharmacology in vivo

The *in vivo* proof of principle experiments have been performed using models of type 2 immune responses mediated through signalling via IL-13. While some of the *in vitro* data suggest applicability of tralokinumab in treatment of AD, no relevant model of AD (e.g. *ex vivo* or *in vitro* human skin models) was presented in a proof of concept study. Several of the models were performed in mice whereas previously discussed the endogenous mouse IL-13 is not bound by tralokinumab. For these studies, injection of human recombinant IL-13 was used since it can bind the mouse IL-13 receptor and mediate signalling in this manner, however, the activity of human IL-13 at the mouse receptor is less than that of mouse IL-13 at the same receptor.

IL-13 was used to induce inflammation in an air pouch inflammation model in mice. Tralokinumab when administered locally via injection into the air pouch inhibited the infiltration of total leukocytes, eosinophils and monocytic cells in a dose dependent manner. For systemically administered tralokinumab, these effects were only seen at the top dose of 30 mg/kg via intravenous (IV) injection. In addition, in a lung inflammation mouse model, tralokinumab delivered via intraperitoneal injection inhibited airway hyperresponsiveness and eosinophil infiltration.

Further *in vivo* studies in cynomolgus monkeys revealed that tralokinumab suppressed total IgE levels in animals with high baseline levels of IgE but not those with lower levels. In general evaluation of tralokinumab efficacy in a cynomolgus monkey lung allergen challenge model showed a modest effect in reducing lung inflammation in the double, but not single allergen challenge model. In all the studies in cynomolgus monkeys the administration of tralokinumab was via IV injection and no studies have been performed with SC injection, the proposed clinical route of administration.

The study in the mice with the air pouch inflammation model suggested that the infiltration of neutrophils into the area of the air pouch was significantly enhanced at the lowest dose of tralokinumab used. Furthermore, in cynomolgus monkeys given an IV injection of 10 mg/kg of tralokinumab (Study CAT354Rp034) haematology measurements suggested a significant increase in neutrophils at Day 1 post injection. The clinical significance of these effects on neutrophils observation are unknown but the clinical route of administration is SC and the formulation used in these experiments is different from the one used clinically.

Secondary pharmacodynamic studies

No secondary PD studies have been performed which is acceptable for a monoclonal antibody. The tissue cross reactivity performed as part of the toxicology studies suggest no binding of tralokinumab to any of the human tissues investigated. Indeed, as a soluble cytokine, no major tissue expression of IL-13 has been reported in the literature. As an IgG4 antibody, the potential for immune effector functions of antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) are considered to be low which is supported by the binding data which suggested little FcγR binding by tralokinumab.

Safety pharmacology programme

The safety pharmacology studies were performed as part of the repeat dose toxicity studies in cynomolgus monkeys in line with ICH S6 (R1). Clinical examinations revealed no effects on the central nervous, cardiovascular and respiratory systems.

Pharmacodynamic drug interactions

No non-clinical PD drug interactions studies have been conducted.

2.3.3. Pharmacokinetics

Several Enzyme-linked immunosorbent assay (ELISA) methods were developed to measure the levels of free tralokinumab which demonstrated acceptable precision and accuracy. The lower and upper limits of quantitation (LLOQ and ULOQ) for the different methods were in the range of 0.1 µg/ml- 6.4 µg/ml for the IL-13 capture method and 10-1500 ng/ml and 0.6-50 µg/ml for the methods based on anti-idiotype antibody.

For the detection of antibodies against tralokinumab, initially an ELISA method for monkey serum was used. Subsequently, a more sensitive and drug tolerant homogenous electrochemiluminescence (ECL) assay was developed (screening and confirmatory assay) and validated on the Meso Scale Discovery (MSD) platform. The assays were selective and the sensitivity of the screening ECL-based anti-drug antibodies (ADA) assay was 241.2 ng/mL. Drug tolerance assessment showed that 75% and 92% high positive control and low positive control could be detected in the presence of 100 and 10 µg/mL tralokinumab, respectively.

An assessment of the PK following repeated administration was performed as part of the repeat dose toxicity and fertility studies with IV dosing for up to 26-weeks and SC dosing for up to 13-weeks. With weekly IV administration, no significant differences were seen between the sexes and exposure, both C_{max} and AUC, increased in a dose dependent manner from 10 to 100 mg/kg, the top dose used. In the 26-week study, accumulation of 3-6 fold was seen and the $t_{1/2}$ was 12 days for recovery animals. The toxicokinetic measured in pregnant cynomolgus monkeys as part of pre and post-natal development studies were comparable to that seen in non-pregnant females. Significant exposures were detected in the infants suggesting that transplacental distribution occurred.

The clinical route of administration is SC injection, however, the data with this route is more limited and no assessment of the bioavailability has been performed with this route. Nevertheless, the studies performed with this route suggest that absorption is slow with the T_{max} seen between 3 and 5 days post dosing. Furthermore, the exposures measured were in excess of that seen via IV dosing. Data from fertility studies suggested that steady state exposure was reached after 9 weeks. Anti-drug antibodies (ADAs) to tralokinumab were measured and in general were found in few animals, which also included control animals, and were not thought to have affected exposure levels. However, there were some concerns raised by CHMP regarding the reliability of these conclusions taking into account the findings of ADAs in control animals. These are further discussed in the toxicology section.

No dedicated distribution studies have been performed which is considered acceptable for a monoclonal antibody targeting a soluble cytokine. In a PK study the volume of distribution was measured following a single IV administration of 10 mg/kg in cynomolgus monkeys. No differences were seen between the sexes and a volume of distribution of 85 mL/kg was measured. Distribution into the breast milk has not been studied but considering that tralokinumab is an IgG4 antibody it would be expected to be low.

Tralokinumab is a large protein above the glomerular filtration cut-off threshold and primarily eliminated by proteolytic catabolism that results in smaller peptides and amino acids. Therefore, no studies on metabolism or excretion have been completed in line with the recommendations of ICH S6 (R1). Similarly, as a monoclonal antibody tralokinumab is not subject to cytochrome (CYP) mediated metabolism.

2.3.4. Toxicology

The toxicity studies have been performed in line with the requirements of ICH S6 (R1) using cynomolgus monkeys as the single species in which there is relevant pharmacological activity. As elucidated in the pharmacology studies, the activity of tralokinumab against IL-13 of cynomolgus monkey origin is similar to that of human origin whilst no relevant activity of tralokinumab was seen against rodent IL-13.

The pivotal toxicology studies with toxicokinetic analyses were performed in compliance with Good Laboratory Practice (GLP) regulations.

Single dose toxicity

In accordance with ICH S6(R1) recommendation, no dedicated single-dose toxicity studies were conducted with tralokinumab. However, no acute toxicity after the first dose was observed at doses up to 100 mg/kg IV in the repeat-dose toxicity studies in the cynomolgus monkey.

Repeat dose toxicity

The repeat dose toxicity studies included 4-, 13- and 26-weeks studies with weekly IV dosing at levels up to 100 mg/kg and weekly SC injections of up to 350 mg/injection for 4- and 13-weeks. The highest dose used in all studies was the No Observed Effect Level (NOEL) and no tralokinumab related adverse toxicities were noted suggesting that tralokinumab was well tolerated. Whilst there were no apparent tralokinumab related effects in these studies, this could be explained by very low circulating IL-13 levels in naïve monkeys. Affinity experiments suggest that tralokinumab has comparable activity against cynomolgus monkey IL-13 to that against human IL-13.

The repeat dose toxicity studies using the SC route of administration are limited to a 28-day bridging study and a 13-week study with weekly administration. Given that this is the intended route of administration, it would typically be expected that a chronic repeat dose toxicity study would be included via the planned clinical route. However, the absence of this study is mitigated by a chronic study of 26-weeks duration via IV infusion in which no tralokinumab related adverse events were noted. Furthermore, the dosing regimen used in the repeat dose toxicity studies using weekly administration is more frequent than the indicated clinical posology of Q2W.

Electrocardiogram (ECG) measurements were performed for all of the IV and SC studies; however, the interval data (P-R, QRS, Q-T waves) were only evaluated in the 26-week IV and 13-week SC studies. No tralokinumab related effects were seen on heart rate, blood pressure or P-R, QRS and Q-T waves. In addition, the 26-week study included an immunophenotyping assessment which indicated that tralokinumab did not significantly modulate any of the immune cell populations investigated which including CD4 and CD8 T cells, NK cells and mature B cells.

There are several instances of measured levels of ADAs to tralokinumab in control animals and even measured levels of tralokinumab in the control group in the 13-week study, although the measured levels are low. The study report suggests that these were isolated instances which were likely sample contaminations and the animals were not exposed to tralokinumab.

The 4-week SC study did have an increased incidence and severity of liver and kidney fat staining. These findings have been suggested to be common findings in cynomolgus monkeys which is supported by historical control data.

The toxicokinetics measured demonstrated no consistent sex differences and exposures generally increased in a dose dependent manner with accumulation levels of 3-6 fold after repeated administration. The presence of ADA to tralokinumab were seen infrequently and not in all studies. Due to high systemic levels of tralokinumab, not all tralokinumab-treated animals could be included for ADA assessment in all studies and ADAs were found in control animals of several studies (1348/058 and 509615). However, systemic exposure levels do not appear to have been affected by the ADAs. There is a margin of exposure of > 10 fold from the NOEL in all of the studies based on C_{max} and AUC comparisons.

Genotoxicity

No studies have been performed in accordance with ICH S6(R1).

Carcinogenicity

No carcinogenicity studies have been performed and considering the lack of activity against IL-13 of rodent origin, traditional rodent studies are not possible. In line with ICH S6 (R1), a weight of evidence approach has been provided which suggests that there are no identified concerns for increased carcinogenic risk with the use of tralokinumab. This is based on the absence of any signal from the toxicity studies to suggest pre-neoplastic changes and no evidence of immune suppression. The data from the literature has conflicting reports of both anti-tumorigenic and pro-tumorigenic effects of IL-13 but on balance the majority of studies suggest a pro-tumorigenic effect suggesting that inhibition of IL-13 is not likely to result in increased malignancy.

Reproduction Toxicity

Due to the lack of activity in rodents, fertility studies were performed as separate male and female fertility studies in sexually mature cynomolgus monkeys using SC injections. Due to the fact that the studies involved the use of monkeys, the assessments were limited to macroscopic/microscopic analysis of the reproductive organs as well as semen evaluation in males and menstrual cycle in females with no mating performed or measurement of reproductive outcomes. Although the absolute doses used were higher in males (600 mg) than in females (350 mg) the exposures achieved were similar. No tralokinumab mediated effects were seen on any of the reproductive organs or the semen evaluation in males and menstrual cycle in females. At the NOEL in both studies there is a margin of exposure for males of 33 and 16 fold the C_{max} and AUC respectively and 37 and 18 fold for females.

A pilot embryo-foetal development toxicity study (Study SNBL.200.07) with once weekly IV infusion of tralokinumab doses at 0, 10, 30 or 100 mg/kg was conducted in pregnant cynomolgus monkeys. Doses were given weekly between Gestational Day (GD) 20 to 48 for a total of 5 administrations with no tralokinumab related effects on foetal toxicity or teratogenicity.

Two enhanced pre- and postnatal development (ePPND) studies were performed due to the fact that the initial study only monitored the F1 generation until PND 28-31. Both studies were performed using IV administration and using the same doses of 30 and 100 mg/kg. The second study monitored the offspring until Day 180 post-partum and included some additional endpoints of neurobehavioral evaluation and a T-cell Dependent Antibody Response (TDAR) following keyhole limpet hemocyanin (KLH) challenge. In both studies there was no evidence that tralokinumab affected the number of embryo-foetal losses or stillbirth rates with the levels measured similar to that of the control groups or within the historical incidence data from the research facility. In the initial study, at the top dose group a shorter gestation length was noted of 155 days compared to 160 days in the controls. Following on

from this, the means birth weight was reduced by ~15% in this group, although body weight gain was comparable to controls in this group after Week 5. This effect on gestation length was not seen in the second PPND study. No adverse effects, on the F1 neonates, were seen in either study on any of the developmental parameters, neurobehavioral evaluations or TDAR response to KLH challenge. There was clear evidence of placental transfer in both studies with neonate serum levels measured comparable or even in excess of maternal levels. In the second PPND detectable levels of tralokinumab were seen on Day 91 post-partum but was mostly below the detection limit at Day 180. At the NOEL of 100 mg/kg in the second study the margins of exposure to that of the clinical dose of 300 mg Q2W are 44 fold for C_{max} and 17 fold for AUC.

Local Tolerance

A stand-alone local tolerance study was conducted in rabbits. There was no differences in the scoring of the injection sites for erythema and eschar formation or oedema formation between sites administered tralokinumab or control vehicle. Histological findings of inflammatory cell infiltration, myositis and myofibre necrosis at the injection sites were observed for both sites receiving tralukinumab and the control. These were minimal in nature and in-line with what would be expected for this route of administration.

Other toxicity studies

No stand-alone immunotoxicity studies were performed. Relevant endpoints for the assessment of potential immunotoxicity were included in the repeat dose toxicity studies. Immunophenotyping suggested no differences in the cell populations investigated following tralokinumab treatment. In addition, no consistent significant differences in TDAR responses to Keyhole limpet haemocyanin (KLH) immunisation were seen in the male and female fertility studies in adult animals or in infants in the PPND. The totality of the data generated in the toxicity studies in terms of haematological analysis, immune organ weight and histopathological response suggested no effects on immune response following tralokinumab treatment. A weight of evidence-based assessment identified a theoretical potential safety risk of helminthic infections based on the role of IL-13 in the type-2 immune response to helminths, however, there was no evidence of such infections in the non-clinical studies to date.

2.3.5. Ecotoxicity/environmental risk assessment

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, tralokinumab is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

Pharmacology

The non-clinical proof of concept studies for the use of tralokinumab in the treatment of AD were largely limited to *in vitro* studies which suggested that in cultured keratinocytes and dermal fibroblasts the use of tralokinumab can prevent IL-13 induction of inflammatory mediators and modulation of genes involved in the maintenance of the skin barrier. The characterisation of the cross-reactivity of tralokinumab against IL-13 from the non-clinical species was limited, however, binding affinity data has been provided for both human and cynomolgus monkey IL-13. Some functional experiments measuring IL-13 mediated cell proliferation have provided evidence of activity against IL-13 of monkey

origin but not of mouse IL-13. Although such data has not been provided, it seems reasonable to assume that tralokinumab will not bind rat IL-13 considering its sequence homology to human IL-13 is 62%, which is in the range of that seen for mouse IL-13 (55%).

While some of the *in vitro* data suggest the applicability of tralokinumab in treatment of AD, no relevant model of AD (e.g. *ex vivo* or *in vitro* human skin models) was presented in a proof of concept study. The *in vivo* experiments are limited and were likely designed with an indication for the treatment of asthma, which was originally one of the clinical indications pursued for tralokinumab. Nevertheless, they do provide some limited evidence that the use of tralokinumab can modulate several aspects of a disease associated with a type II immune response. In murine models of inflammation, tralokinumab could inhibit inflammatory responses induced by hIL-13 and hIL-13 and murine IL-13 were able to elicit pro-inflammatory effects in mouse models and human cell-lines (i.e. TF-1) respectively. In the air pouch inflammation model, there was a finding of increased neutrophil infiltration into the local area when tralokinumab was injected into the air pouch, although only at the lowest dose of tralokinumab and considering the differences in the route and formulation used clinically, this is not considered of significant clinical relevance by CHMP.

Pharmacokinetics

Limited PK studies have been performed with the majority of the PK data derived from the toxicokinetics collected as part of the repeat dose toxicity studies in cynomolgus monkey. Such an approach is appropriate for a monoclonal antibody. No assessment of bioavailability has been performed following SC administration. However, the exposures measured using this route of administration are comparable to that seen using IV dosing at similar dose levels suggesting a high level of bioavailability using this route and therefore such studies are not considered to be necessary.

The absence of *in vitro* drug-interaction studies was accepted by the CHMP.

Toxicology

The provided non-clinical toxicology studies are in line with the relevant ICH S6(R1) guideline. Tralokinumab was well tolerated in all repeat dose studies which is reflected in the absence of any adverse events (AEs) noted in the studies of up to 26-weeks via IV dosing and 13-weeks via SC injection. There were no apparent tralokinumab related effects in these studies which could be explained by very low circulating IL-13 levels in naïve monkeys. Nevertheless, it is arguable that ICH S6 (R1) suggests a chronic toxicity study of 26-weeks via the clinical route of administration i.e. SC injection would have been expected. The only chronic study provided is a 26-week study with IV dosing. However, considering that the chronic study is via IV dosing and the absence of tralokinumab related findings in this study, as well as the 13-week study via SC injection, suggests that a 26-week SC study would be of limited value for providing further safety information. Indeed, the margin of exposure from the NOEL, identified in the 13-week SC injection repeat dose toxicity study, to the clinical exposure levels at the proposed posology of 300 mg Q2W is ~ 33 fold.

The report of the 13-week study suggested that the levels of ADAs to tralokinumab were isolated instances which were likely sample contaminations and the animals were not exposed to tralokinumab. This justification was accepted by CHMP.

The 4-week SC study did have an increased incidence and severity of liver and kidney fat staining, however, there were significant deficiencies in this bridging study since no control groups were utilised and the study was only performed using male animals. These findings have been suggested to be common findings in cynomolgus monkeys which is supported by historical control data.

A comprehensive assessment of the reproductive toxicity potential of tralokinumab have also been performed. Animals in the 26-week repeat-dose toxicity study were relatively young (13-19 months)

and therefore not sexually mature. Similarly, animals in the other repeat dose studies were not sexually mature. It is understood that this would be a rationale for conducting the male fertility study. It is also acknowledged that identifying sexually mature test animals for toxicology studies is not without its difficulties[9]. However, in line with ICH S6 and basic 3R principles, selecting a more mature test population in at least one pivotal toxicology study would exclude the need for further specific studies since the selected endpoints could have been assessed there as well. CHMP also agreed that the effect seen on gestational length seen in the initial PPND study is unlikely to be related to tralokinumab treatment. The results of the toxicity studies are reflected in section 5.3 'Pre-clinical safety data' of the SmPC.

2.3.7. Conclusion on the non-clinical aspects

Overall the provided non-clinical package is sufficient to support the MAA for tralokinumab in AD.

2.4. Clinical aspects

2.4.1. Introduction

The clinical development programme included 5 clinical studies in AD: a phase 2b dose-finding study (D2213C00001), 2 phase 3 monotherapy efficacy and safety studies (ECZTRA 1 and 2), a phase 3 combination therapy efficacy and safety study (ECZTRA 3) and a phase 2 vaccine response study (ECZTRA 5).

Furthermore, 3 clinical studies in healthy subjects and 14 clinical studies from the clinical development programmes in other indications are considered of relevance for safety and PK in the AD development programme and therefore relevant results are summarised in the report where relevant.

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant 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.

Table 1 Tabular overview of clinical studies

[9] Luetjens, C. M., Weinbauer, G. F. (2012). Functional assessment of sexual maturity in male macaques (*Macaca fascicularis*). Regul Toxicol Pharmacol 63, 391–400.

Type of trial **Objectives**	**Trial ID** **Trial status** **Type of report**	**Trial design**	**FSFV** **LSLV** **Site number & location**	**Planned/randomised/ exposed/completed subjects** **Median age (range)** **Sex**	**Main inclusion criteria and diagnosis**	**IMPs, dose, route & regimen (n, exposed subjects)**	**Treatment duration**	**Primary endpoints**
Phase 2b Dose-finding Efficacy, safety, PK, immuno-genicity	D2213C00001 Completed Full CTR	Randomised (1:1:1:1), double-blind, placebo-controlled, parallel-group Multiple dose, combination therapy	23-Jan-2015 05-Feb-2016 55 sites in AUS, DEU, JPN, POL, CAN, USA	184/204/204/170 34.0 years (18–74) M: 110 (53.9%) F: 94 (46.1%)	Adults (18–75 years) with moderate-to-severe AD: - AD of ≥10% BSA (EASI) - EASI score ≥12 - SCORAD ≥25 - IGA score ≥3	Tralokinumab 2 mL, SC[a], Q2W+TCS: - 45 mg (n=50, 6 Japanese) - 150 mg (n=51, 6 Japanese) - 300 mg (n=52, 7 Japanese) Placebo 2 mL, SC[a], Q2W+TCS (n=51, 6 Japanese)	12 weeks (6 doses, last dose Week 10)	Hierarchical testing: - Absolute change from baseline in EASI at Week 12 - Percentage of subjects achieving IGA 0 (clear) or 1 (almost clear) and at least a 2-grade reduction from baseline at Week 12

Phase 3 Efficacy and safety	ECZTRA 1 (LP0162-1325) Completed Full CTR	Initial treatment Randomised (3:1), double-blind, placebo-controlled Multiple dose, monotherapy The initial treatment period continued into a maintenance treatment period, where tralokinumab responders[b] were re-randomised (2:2:1), placebo responders[b] continued placebo treatment, and non-responders[b] entered an open-label arm[c].	30-May-2017 18-Jul-2019 115 sites in FRA, DEU, JPN, ESP, USA	Initial treatment 780/802/798/729 37.0 years (18–92) M: 474 (59.1%) F: 328 (40.9%) Maintenance treatment *Tralokinumab and placebo responders[b]* NA/NA/208/133 Open-label *(non-responders[b])* NA/NA/563/446	Adults (≥18 years) with moderate-to-severe AD, candidates for systemic therapy: - AD of ≥10% BSA - EASI score ≥12 at screening and ≥16 at baseline - IGA score ≥3 - WDP NRS average score ≥4	Initial treatment - Tralokinumab 300 mg, SC[a], Q2W, after 600 mg initial loading (n=602, 96 Japanese) - Placebo 2 mL, SC[a], Q2W, after 4 mL initial loading (n=196, 31 Japanese) Maintenance treatment *Tralokinumab responders[b] re-randomised (2:2:1)* - Tralokinumab 300 mg, SC[a], Q2W (n=68) - Tralokinumab 300 mg, SC[a], Q4W[d] (n=76) - Placebo 2 mL, SC[a], Q2W (n=35) *Placebo responders[b]* - Placebo 2 mL, SC[a], Q2W (n=29) Open-label *(non-responders[b])* Open-label[c] tralokinumab 300 mg, SC[a], Q2W+optional TCS (n=563)	Initial treatment 16 weeks Maintenance and open-label treatment +36 weeks (total period: 52 weeks, last dose Week 50)[e]	Superiority hierarchical testing (initial treatment): - IGA 0/1 at Week 16 - EASI75 at Week 16

Phase 3 Efficacy and safety	ECZTRA 2 (LP0162-1326) Completed Full CTR	Initial treatment Randomised (3:1), double-blind, placebo-controlled Multiple dose, monotherapy The initial treatment period continued into a maintenance treatment period, where tralokinumab responders[b] were re-randomised (2:2:1), placebo responders[b] continued placebo treatment, and non-responders[b] entered an open-label arm[c].	29-Jun-2017 14-Aug-2019 104 sites in AUS, CAN, DNK, GBR, ITA, KOR, POL, RUS, USA	Initial treatment 780/794/792/737 33.0 years (18–86) M: 473 (59.6%) F: 321 (40.4%) Maintenance treatment *Tralokinumab and placebo responders[b]* NA/NA/257/133 Open-label *(non-responders[b])* NA/NA/558/423	Adults (≥18 years) with moderate-to-severe AD, candidates for systemic therapy: - AD of ≥10% BSA - EASI score ≥12 at screening and ≥16 at baseline - IGA score ≥3 - WDP NRS average score ≥4	Initial treatment - Tralokinumab 300 mg, SC[a], Q2W, after 600 mg initial loading (n=592) - Placebo 2 mL, SC[a], Q2W, after 4 mL initial loading (n=200) Maintenance treatment *Tralokinumab responders[b] re-randomised (2:2:1)* - Tralokinumab 300 mg, SC[a], Q2W (n=91) - Tralokinumab 300 mg, SC[a], Q4W[d] (n=89) - Placebo 2 mL, SC[a], Q2W (n=46) *Placebo responders[b]* - Placebo 2 mL, SC[a], Q2W (n=31) Open-label *(non-responders[b])* Open-label[c] tralokinumab 300 mg, SC[a], Q2W+optional TCS (n=558)	Initial treatment 16 weeks Maintenance and open-label treatment +36 weeks (total period: 52 weeks, last dose Week 50)	Superiority hierarchical testing (initial treatment): - IGA 0/1 at Week 16 - EASI75 at Week 16

Phase 3 Efficacy and safety	ECZTRA 3 (LP0162-1339) Completed Full CTR	<u>Initial treatment</u> Randomised (2:1), double-blind, placebo-controlled Multiple dose, combination therapy The initial treatment period continued into a <u>continuation treatment</u> period, where tralokinumab responders[b] were re-randomised (1:1), placebo responders[b] continued placebo treatment, and non-responders[b] received tralokinumab+ TCS treatment.	27-Feb-2018 26-Jun-2019 65 sites in BEL, CAN, DEU, NLD, POL, ESP, GBR, USA	<u>Initial treatment</u> 369/380/378/355 36.0 years (18–80) M: 209 (55.0%) F: 171 (45.0%) <u>Continuation treatment</u> NA/NA/353/330	Adults (≥18 years) with moderate-to-severe AD, candidates for systemic therapy: - AD of ≥10% BSA (SCORAD) - EASI score ≥12 at screening and ≥16 at baseline - IGA score ≥3 - WDP NRS average score ≥4	<u>Initial treatment</u> - Tralokinumab 300 mg, SC[a], Q2W+TCS, after 600 mg initial loading (n=252) - Placebo 2 mL, SC[a], Q2W+TCS, after 4 mL initial loading (n=126) <u>Continuation treatment</u> *Tralokinumab responders[b] re-randomised (1:1)* - Tralokinumab 300 mg, SC[a], Q2W+TCS (n=69) - Tralokinumab 300 mg, SC[a], Q4W[d]+TCS (n=69) *Placebo responders[b]* - Placebo 2 mL, SC[a], Q2W+TCS (n=41) *Non-responders[b]* - Tralokinumab 300 mg, SC[a], Q2W+TCS (n=174)	<u>Initial treatment</u> 16 weeks <u>Continuation treatment</u> +16 weeks (total period: 32 weeks, last dose Week 30)	Superiority hierarchical testing (initial treatment): - IGA 0/1 at Week 16 - EASI75 at Week 16

Type of trial Objectives	Trial ID Trial status Type of report	Trial design	FSFV LSLV Site number & location	Planned/randomised/ exposed/completed subjects Median age (range) Sex	Main inclusion criteria and diagnosis	IMPs, dose, route & regimen (n, exposed subjects)	Treatment duration	Primary endpoints
Phase 2 Vaccine response	ECZTRA 5 (LP0162-1341) Completed Full CTR	Randomised (1:1), double-blind, placebo-controlled Multiple dose, monotherapy 1 dose of Tdap and meningococcal vaccines IM at Week 12 for evaluation of primary endpoints	13-Jul-2018 22-Nov-2019 46 sites in CAN and USA	200/215/214/190 32.0 years (18–54) M: 89 (41.4%) F: 126 (58.6%)	Adults (18–54 years) with moderate-to-severe AD, candidates for systemic therapy: - AD of ≥10% BSA (SCORAD) - EASI score ≥12 at screening and ≥16 at baseline - IGA score ≥3	- Tralokinumab 300 mg, SC[a], Q2W, after 600 mg initial loading (n=107) - Placebo 2 mL, SC[a], Q2W, after 4 mL initial loading (n=107)	16 weeks (last dose Week 14)	Non-inferiority hierarchical testing: - Positive anti-tetanus response at Week 16 - Positive meningococcal response at Week 16

Type of trial Objectives	Trial ID Trial status	Trial design	Planned number of subjects	Main inclusion criteria and diagnosis	IMPs, dose, route & regimen	Treatment duration	Primary endpoints
Phase 1 Drug-drug interaction	ECZTRA 4 (LP0162-1342) Ongoing	Open-label, drug-drug interaction, multicentre Pre-IMP period of 7 days; substrate cocktail (selected CYP P450 substrates) administered on Day -7 (baseline). IMP-period of 16 weeks; substrate cocktail administered on Day 8 and Week 15.	40	Adults (≥18 years) with moderate-to-severe AD, candidates for systemic treatment: - AD of ≥10% BSA - EASI score ≥12 at screening and ≥16 at baseline - IGA score ≥3	Tralokinumab 300 mg, SC, Q2W, after 600 mg initial loading	16 weeks (last dose Week 14)	For each of the 5 substrates (caffeine, metoprolol, midazolam, omeprazole, and warfarin), ratios between measures after multiple doses of tralokinumab (MD) and baseline with no tralokinumab dose (Base) for: - $AUC_{last,MD}$:$AUC_{last,Base}$ - $C_{max,MD}$:$C_{max,Base}$

Phase 3 Efficacy and safety	ECZTRA 6 (LP0162-1334) Ongoing	Initial treatment Randomised (1:1:1), double-blind, placebo-controlled, parallel-group, multicentre Monotherapy The initial treatment period continued into a maintenance treatment period, where tralokinumab responders[f] were re-randomised (1:1), placebo responders[f] continued placebo treatment, and non-responders[f] entered an open-label arm[g].	Initial treatment 294	Adolescents (12–17 years) with moderate-to-severe AD, candidates for systemic treatment: - AD of ≥10% BSA - EASI score ≥12 at screening and ≥16 at baseline - IGA score ≥3	Initial treatment - Tralokinumab 300 mg, SC, Q2W, after 600 mg initial loading - Tralokinumab 150 mg, SC, Q2W, after 300 mg initial loading - Placebo 2 mL, SC, Q2W, after 4 mL initial loading Maintenance treatment *Tralokinumab 300 mg responders[f] re-randomised (1:1)* - Tralokinumab 300 mg, SC, Q2W - Tralokinumab 300 mg, SC, Q4W[h] *Tralokinumab 150 mg responders[f] re-randomised (1:1)* - Tralokinumab 150 mg, SC, Q2W - Tralokinumab 150 mg, SC, Q4W[h] *Placebo responders[f]* - Placebo 2 mL, SC, Q2W Open-label *(non-responder[f])* Open-label[g] tralokinumab 300 mg, SC, Q2W+optional TCS	Initial treatment 16 weeks Maintenance and open-label treatment +36 weeks (total period: 52 weeks, last dose Week 50)	Hierarchical testing (initial treatment): - IGA 0/1 at Week 16 - EASI75 at Week 16

Type of trial Objectives	Trial ID Trial status	Trial design	Planned number of subjects	Main inclusion criteria and diagnosis	IMPs, dose, route & regimen	Treatment duration	Primary endpoints
Phase 3 Efficacy and safety	ECZTRA 7 (LP0162-1346) Ongoing	Randomised (1:1), double-blind, placebo-controlled, parallel-group, multicentre Combination therapy	250	Adults (≥18 years) with severe AD, ineligible for oral CSA: - AD of ≥10% BSA - EASI score ≥20 - IGA score ≥3 - WDP NRS average score ≥4	- Tralokinumab 300 mg, SC, Q2W, after 600 mg initial loading+TCS - Placebo 2mL, SC, Q2W, after 4 mL initial loading+TCS	26 weeks (last dose Week 24)	EASI75 at Week 16
Phase 3 Long-term extension trial Efficacy and safety	ECZTEND (LP0162-1337) Ongoing	Open-label, single-arm, multicentre, long-term extension trial Combination therapy Home injection	1125	Subjects with AD from some countries who had completed the treatment period of one of the tralokinumab trials ECZTRA 1 to 5 and 7	Tralokinumab 300 mg, SC, Q2W, after 600 mg initial loading+TCS or TCI at investigators discretion	1.5 to 2.5 years (treatment stop 31-May-2021)	Number of AEs from baseline to last treatment visit (≤Week 142)

Notes: *[a]SC administration was done using a syringe and vial with 150 mg/mL tralokinumab in the dose-finding trial D2213C00001, and using a pre-filled, single-use, disposable syringe with 1 mL of 150 mg tralokinumab/mL in ECZTRA 1, 2, 3 and 5. [b]Responders in ECZTRA 1, 2 and 3 were defined as subjects with clinical response defined as IGA of 0 or 1, or at least 75% reduction in EASI score from baseline (EASI75) at Week 16. [c]The open-label arm in ECZTRA 1 and 2 included subjects without clinical response[a] at Week 16 from both tralokinumab and placebo groups. In addition, subjects in maintenance treatment who met certain criteria of non-responders could transfer to open-label treatment from Week 22. [d]In the tralokinumab 300 mg, SC, Q4W groups in ECZTRA 1, 2, and 3, subjects were treated Q2W with alternating dose of tralokinumab and placebo. [e]In ECZTRA 1, some subjects from Japan continued for additional 16 weeks with open-label treatment to a total period of 68 weeks (last dose Week 66). [f]Responders in ECZTRA 6 were defined as subjects with clinical response defined as IGA of 0 or 1, or at least 75% reduction in EASI score from baseline (EASI75) at Week 16 without use of rescue treatment from Week 2 to Week 16. [g]The open-label arm in ECZTRA 6 included subjects without clinical response[f] at Week 16 from both tralokinumab and placebo groups. In addition, subjects in maintenance treatment, who met certain criteria of non-responders could transfer to open-label treatment. [h]In the tralokinumab SC, Q4W arms in ECZTRA 6, subjects were treated Q2W with alternating dose of tralokinumab and placebo.*

2.4.2. Pharmacokinetics

The PK of tralokinumab was evaluated in 11 studies: 4 phase 1 studies, 4 phase 2 studies and 3 phase 3 studies.

During the phase 1 studies, intensive PK sampling was applied. The other studies had only a sparse sampling schedule. The applicant developed a popPK model including all relevant PK data. Tralokinumab was administered only SC and IV and various doses were used throughout these studies. Tralokinumab was initially developed for treatment of asthma and therefore PK parameters have also been presented from studies in patients with asthma.

Bioanalytical methods

Tralokinumab serum concentration

Two different assays were used during clinical development to measure serum concentration of tralokinumab. A direct ELISA method was used during the phase I study CAT-354-0401 (asthma) and a sandwich immunoassay (Gyrolab platform) was used for all subsequent studies.

The results from CAT-354-0401 provide data regarding linearity, basic PK parameters and dose proportionality. However, data obtained from subsequent clinical trials also contributes to this information. Data has been presented to support that appropriate method controls were in place at the time of assay performance. A summary of the validation results for this assay was provided and method suitability has been adequately demonstrated.

The sandwich immunoassay (Gyrolab platform) used to evaluate samples from all subsequent trials was performed at three separate laboratories (MedImmune, LGC Ltd. and Covance Ltd.). Method validation reports have been provided from each laboratory. Method re-validation was performed upon the introduction of new reagents (including a new sample diluent) however, no significant changes were introduced to the method. The data provided supports equivalent performance of the method at each site.

The method has been validated in line with the guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev 1) to address accuracy, precision, linearity, dilutional linearity, limit of quantification, tolerance (impact of ADA antibodies on assay performance), stability of reagents and sample stability. The tolerance of the method has been established at 10.0 ng/ml ADA and data has been presented to support that tralokinumab exposures for subjects showing positive ADA responses is comparable to the geometric mean exposure in patients showing negative ADA responses. This indicates a lack of interference from ADA. It has been confirmed that samples were processed and stored in accordance with the established conditions for which stability has been demonstrated. The results of incurred samples reanalysis were provided for LGC Ltd. and Covance and demonstrated that the method provided consistent results.

ADA assays

In accordance with the draft Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev.1), the presence of ADAs were evaluated using the recommended three tiered approach: an initial screening assay to identify potentially ADA positive samples, a confirmation assay based on competition with exogenously added tralokinumab and a determination of the titre of ADA for confirmed positive samples.

Three ADA assays were used during development; the original AstraZeneca ADA assay, the updated AstraZeneca ADA assay and the LEO ADA assay. Only the updated AstraZeneca ADA assay and the

LEO ADA assays were used for testing serum samples from AD studies and therefore these methods were the main focus of assessment.

The ADA assay was based on the MSD platform where ADAs form a bridge between biotinylated tralokinumab and sulfo-tagged tralokinumab which is detected by measuring the resulting chemiluminescent signal. The confirmation assay used an excess of unlabelled tralokinumab. For the titre assay, samples are serially diluted to identify the highest dilution still giving a positive signal.

For both ADA assays, the establishment of the screening and confirmation assay cut-points were explained. The positive control was a mouse monoclonal antibody which showed neutralising activity against tralokinumab. Different false positive rates were used for determination of the confirmation cut-point in both assays, however the Applicant has justified that this did not lead to any differences in the positivity rate.

For both assays appropriate details of method validation were provided. The assays were validated for intra-assay precision, inter-assay precision, sensitivity, drug tolerance, selectivity, hook effect, and stability.

Both ADA assays were shown to be sufficiently precise with CVs ≤25%. While the sensitivity of the assays is considered acceptable, at the therapeutic dose, the upper range for $\sim C_{max}$ (mid-dosing interval concentration at Week 15) in the ECZTRA 1 trial was 341 ug/ml, compared to the demonstrated assay tolerance of 200 µg/ml. Overall, 64 samples tested for ADA had tralokinumab serum concentrations > 200 µg/mL. This corresponds to 0.2 – 0.8% of all ADA samples from ECZTRA 1, 2, 3 and 5.

NAb assays

The neutralising antibodies (Nab) assay used a ligand binding format and, as for the ADA assays, two separate NAb assays were developed, the LEO NAb assay and the Updated AZ NAb assay. The Applicant highlighted that a cell-based format was also explored but that the sensitivity was not sufficient. It is therefore acceptable to measure NAb using a ligand binding assay. The assay is based on the competition of NAbs with IL-13 for tralokinumab binding.

Details of the determination of cut-points have been provided, using serum from AD subjects. The NAb assays were validated for intra-assay precision, inter-assay precision, sensitivity, drug tolerance, selectivity, hook effect and stability.

The assays were shown to have a sufficient level of precision at CV ≤20%. At the low positive control level, the LEO NAb assay was intolerant to tralokinumab. However, the Applicant has justified that the assay is capable of detecting NAb positive samples in the presence of levels of tralokinumab. up to 164 µg/mL. This is in excess of the experimentally determined tolerance of 25 µg/ml using the mouse monoclonal positive control antibody. It can therefore be accepted that the presence of tralokinumab in samples is unlikely to have a large impact on the false negative rate.

Population PK analysis

Tralokinumab serum concentration–time data collected from 10 clinical trials, including 3 phase 1 trials (CAT-354-0703, MI-CP224, and CAT-354-0602), 4 phase 2 trials (MI-CP199, CD-RI-CAT-354-1049, D2213C00001, and ECZTRA 5) and 3 phase 3 trials (ECZTRA 1, ECZTRA 2, and ECZTRA 3), were used for the popPK analysis of tralokinumab in healthy subjects, subjects with asthma, and subjects with AD following IV or SC administration. The combined dataset included 13,361 serum concentrations of tralokinumab from 2,561 subjects.

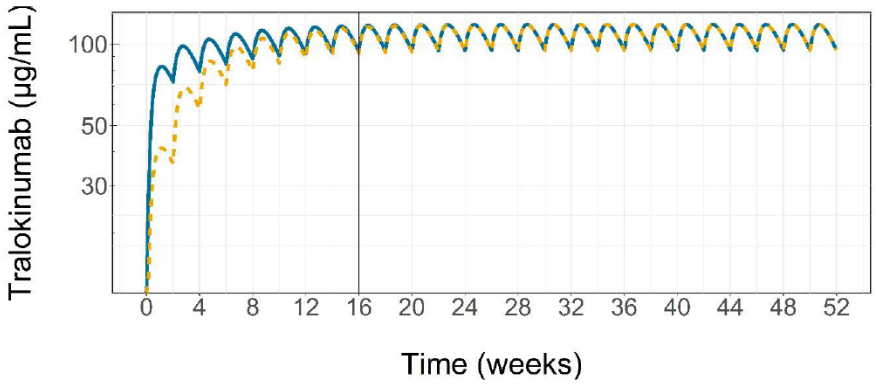
The final popPK model was a 2-compartment model with first-order absorption and elimination from the central compartment, with log-normal IIV on volume (V2) and clearance (CL), and a combined

additive and proportional error model. Covariates included in the final model were body weight on volume (V2 and V3) and clearance (CL and Q) with estimated allometric exponents of 0.783 and 0.873, respectively, non-ECZTRA trials on V2 and CL, and dilution on F and ka.

The final popPK model was used for a series of simulations including evaluating the influence of a loading dose on the time to reach steady state and comparing tralokinumab exposure after multiple dosing of 300 mg Q2W with 300 mg Q4W.

- ***Impact of a loading dose on time to reach steady state***

The concentration–time profile was simulated for a typical subject dosed with tralokinumab 300 mg Q2W with and without a 600 mg loading dose. Steady state (90% of steady state) is predicted to be reached at Week 6 *with* a loading dose and at Week 10 *without* a loading dose (Figure 1).

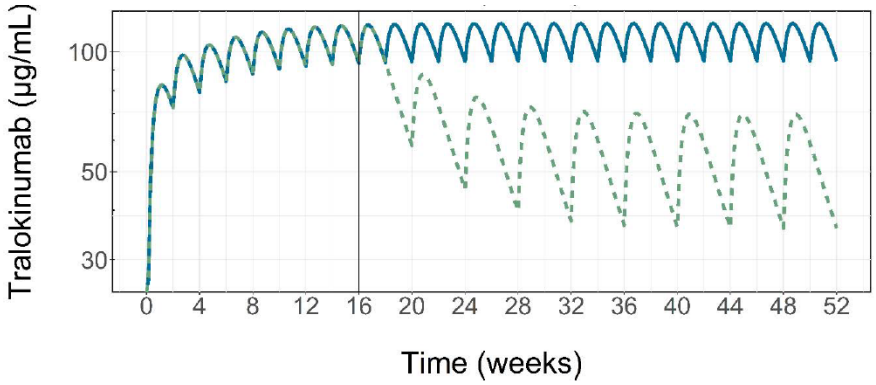


Top: Simulations of the concentration–time profile for a typical subject (weighing 75 kg) following subcutaneous administration of tralokinumab 300 mg every second week *with* (blue solid line) and *without* (yellow dashed line) a 600 mg loading dose. Derived from the final population PK model.

Figure 1 Final model: Simulations of PK for a typical subject

- ***Predicted tralokinumab exposure with 300 mg Q2W and 300 mg Q4W***

PK simulations were performed for a typical subject dosed with tralokinumab 300 mg Q2W for 52 weeks, and for a typical subject dosed with tralokinumab 300 mg Q2W for 16 weeks followed by tralokinumab 300 mg Q4W until Week 52 (Figure 2).



Bottom: Simulations of the concentration–time profile for a typical subject (weighing 75 kg) following subcutaneous administration of tralokinumab 300 mg every second week (with a loading dose of 600 mg) for 52 weeks (blue solid line), or tralokinumab 300 mg every second week (with a loading dose of 600 mg) for 16 weeks followed by tralokinumab 300 mg fourth week until Week 52 (green dashed line). Derived from the final population PK model.

Figure 2 Final model: Simulations of PK for a typica subject

Absorption

Healthy volunteers' studies

Study MI-CP224 was a phase 1 randomised, single-blind, placebo-controlled, single ascending dose study in healthy Japanese men and women, conducted at a single site in the USA. Three dose levels of tralokinumab (150 mg, 300 mg, and 600 mg) were studied in 3 sequential dose cohorts. Within each dose cohort, subjects were randomised in an 8:2 ratio to a single SC dose of tralokinumab or placebo. Subjects were followed up for 10 weeks post-dose for assessment of PK, safety, and immunogenicity.

Study CAT-354-0703 was a phase 1 randomised, open-label, parallel-group, single-dose trial in healthy men, conducted at a single site in the USA. Subjects were randomised in a 1:1:1 ratio to a single dose of tralokinumab 150 mg via a 30-minute IV infusion or tralokinumab 150 mg or 300 mg via SC injection. Subjects were followed up for at least 8 weeks post-dose for assessment of PK, safety, and immunogenicity.

The PK parameters are summarised in Table 2 for study MI-CP224 and in Table 3 for study CAT-354-0703.

Table 2 Trial MI-CP224: PK parameters for tralokinumab after a single subcutaneous dose

	Tralokinumab dose group		
Parameter	**150 mg (N=8)**	**300 mg (N=8)**	**600 mg (N=8)**
$AUC_{0-\infty}$, µg×day/mL	732 ± 183	1459 ± 383	3445 ± 1328
C_{max}, µg/mL	23.8 ± 5.5	44.8 ± 8.9	103 ± 21
CL/F, mL/kg/day	3.17 ± 0.56	3.30 ± 0.60	3.14 ± 0.80
t_{max}, days	6.0 (3.0, 7.0)	5.0 (5.0, 9.0)	7.1 (3.0, 9.1)
$t_{½}$, days	20.0 ± 2.1	20.9 ± 2.8	24.6 ± 7.3
V/F, mL/kg	91.1 ± 16.5	98.1 ± 10.2	105 ± 14.5

Note: $AUC_{0-\infty}$ and C_{max} are given as geometric mean ± standard deviation (SD), t_{max} is given as median (minimum, maximum), and other parameters are given as arithmetic mean ± SD.

Abbreviations: $AUC_{0-\infty}$ = area under the serum concentration–time curve from time zero extrapolated to infinity; CL/F = apparent clearance; C_{max} = maximum observed serum concentration after dosing; N = number of subjects; $t_{½}$ = terminal elimination half-life; t_{max} = time to reach C_{max}; V/F = apparent volume of distribution (after subcutaneous dosing).

Table 3 Trial CAT-354-0703: PK parameters for tralokinumab after single intravenous and subcutaneous doses

	Tralokinumab dose group		
Parameter	**150 mg IV (N=10)**	**150 mg SC (N=10)**	**300 mg SC (N=10)**
$AUC_{0-\infty}$, µg×day/mL	855 ± 291	531 ± 143	1030 ± 315
C_{max}, µg/mL	56.8 ± 14.4	16.3 ± 5.9	34.4 ± 13.1
CL or CL/F, mL/kg/day	2.40 ± 0.98	3.34 ± 0.83	3.60 ± 1.07
t_{max} (min, max), days	0.06 (0.04, 1.02)	5 (3, 9)	5 (3, 9)
$t_{½}$, days	21.4 ± 2.5	19.2 ± 3.1	19.4 ± 3.6
V_d, mL/kg	63.6 ± 16.6	ND	ND

Notes: $AUC_{0-\infty}$ and C_{max} are given as geometric mean ± standard deviation (SD), t_{max} is given as median (minimum, maximum), and other parameters are given as arithmetic mean ± SD.

Abbreviations: $AUC_{0-\infty}$ = area under the serum concentration–time curve from time zero extrapolated to infinity; C_{max} = maximum observed serum concentration after dosing; CL = clearance (after IV dosing); CL/F = apparent clearance (after SC dosing); IV = intravenous; N = number of subjects; ND = not determined; SC = subcutaneous; $t_{½}$ = terminal elimination half-life; t_{max} = time to reach C_{max}; V_d = apparent volume of distribution (after IV dosing).

In study CAT-354-0703, the absolute bioavailability of tralokinumab after SC injection - calculated by comparing the $AUC_{0-\infty}$ values - after a single SC dose and a single IV dose was 62% (90% CI: 48.5-79.6) for the 150 mg dose and 60% (90% CI: 46.9-77.1) for the 300 mg dose. It should be noted that the bioavailability might have been underestimated, given that the mean body weight was higher for subjects in the SC group (87.3 ± 8.1 kg) than for subjects in the IV group (78.7 ± 14.7 kg), and that exposure of tralokinumab decreases with increasing body weight, as shown by popPK modelling.

In the popPK analysis, bioavailability of tralokinumab was estimated to 76.1%. The mean $t_{½}$ and CL were similar after both SC doses and the IV dose.

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

In both studies (Study MI-CP224, Study CAT-354-0703) , there was a dose-proportional increase in systemic drug exposure and no ADA were detected in any subjects.

Asthma studies

Study CAT-354-0401 was a phase 1 randomised, double-blind, placebo-controlled, single ascending dose trial in men with mild asthma, conducted at a single site in the UK. Six dose levels of tralokinumab (0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg, and 30 mg/kg) were studied in 6 sequential dose cohorts. Within each cohort, subjects were to be randomised in a 5:1 ratio to a single dose of tralokinumab or placebo, administered as a 30-minute IV infusion. Subjects were followed up for 12 weeks post-dose for assessment of PK, safety, and immunogenicity, and then every 4 weeks until tralokinumab was no longer detectable in serum.

Study CAT-354-0602 was a phase 1 randomised, double-blind, placebo-controlled, multiple-dose trial in adults with moderate asthma, conducted at 2 sites in the UK. Three dose levels of tralokinumab (1 mg/kg, 5 mg/kg, and 10 mg/kg) were studied in 3 sequential dose cohorts. Within each cohort, subjects were to be randomised in an 8:2 ratio to tralokinumab or placebo, administered as a 30-minute IV infusion on 3 occasions, 4 weeks apart. After their last dose, subjects were followed up for 13 weeks for assessment of PK, safety, PD, and immunogenicity.

Study MI-CP199 was a phase 2a randomised, double-blind, placebo-controlled trial, conducted at multiple sites in 5 European countries, in adults with uncontrolled, moderate-to-severe, persistent asthma. 194 subjects were randomised in a 1:1:1 ratio to 3 dose cohorts (tralokinumab 150 mg, 300 mg, or 600 mg SC). Within each cohort, subjects were randomised in a 3:1 ratio to tralokinumab or placebo. Subjects were dosed Q2W for 14 weeks, then followed up for 12 weeks after the last dose for assessment of PK, safety, and immunogenicity.

Study CD-RI-CAT-354-1049 was a phase 2b randomised, double-blind, placebo-controlled trial, conducted at multiple sites in 15 countries, in adults with uncontrolled, severe asthma requiring concomitant treatment with high-dose inhaled corticosteroids and long-acting β2-agonists. 452 subjects were randomised in a 1:1 ratio to 2 cohorts: Q2W for 52 weeks (with last dose at Week 51), or Q2W for 12 weeks followed by Q4W for 40 weeks (Q2/4W, with last dose at Week 49). Within each cohort, subjects were randomised in a 2:1 ratio to tralokinumab 300 mg SC or placebo. Subjects were followed up for 24 weeks after the last dose of Investigational Medicinal Product (IMP) for assessment of PK, safety, and immunogenicity.

The PK parameters are summarised in Table 4 for study CAT-354-0401, Table 5 for study CAT-354-062 and Figure 3 for study MI-CP199.

Table 4 Trial CAT-354-0401: PK parameters for tralokinumab after a single dose intravenous dose

Parameter[a]	Tralokinumab IV dose group					
	0.1 mg/kg[b] (N=3)	0.3 mg/kg (N=5)	1 mg/kg (N=5)	3 mg/kg (N=5)	10 mg/kg (N=5)	30 mg/kg (N=5)
$AUC_{0-\infty}$, µg×day/mL	ND	107 (n=3) ± 8.6	309 ± 68	835 ± 227	3089 ± 344	11688 ± 1912
C_{max}, µg/mL	1.72 ± 0.86	7.64 ± 1.84	23.8 ± 4.5	81.0 ± 18.3	276 ± 61	848 ± 166
CL, mL/kg/day	ND	2.92 (n=3) ± 0.20	3.27 ± 0.71	3.68 ± 1.01	3.25 ±0.35	2.60 ± 0.43
$t_{½}$, days	18.0 (n=2) ± 4.4	32.4 ± 14.2	30.9 ± 8.4	25.3 ± 3.0	33.5 ± 10.1	23.5 ± 1.9
V_d, mL/kg	ND	145 (n=3) ± 48	144 ± 42	132 ± 31	155 ± 45	87.3 ± 11.6

[a] $AUC_{0-\infty}$ and C_{max} are given as geometric mean ± standard deviation (SD); other parameters are given as arithmetic mean ± SD.

[b] The actual dose received by each subject was 45%, 68%, and 116% of the nominal dose (due to rounding of volume to nearest mL, and miscalculation in the dose for 1 subject).

Abbreviations: $AUC_{0-\infty}$ = area under the serum concentration–time curve from time zero extrapolated to infinity; CL = clearance (after IV dosing); C_{max} = maximum observed serum concentration after dosing; IV = intravenous; n = number of subjects with data; N = number of subjects in analysis set; ND = not determined; $t_{½}$ = terminal elimination half-life; V_d = apparent volume of distribution (after IV dosing).

Systemic exposure to tralokinumab, as assessed by C_{max} and $AUC_{0-\infty}$, appeared to increase in a dose-proportional manner for the doses from 0.1 to 10 mg/kg. For the last dose increase from 10 to 30 mg/kg, there was a tendency for supra-proportional increase in $AUC_{0-\infty}$. 1 subject had a positive result for ADAs pre-dose but not post-dose. No subject had a negative pre-dose and positive post-dose sample. Thus, there was no evidence of immunogenicity induced by tralokinumab.

Table 5 Trial CAT-354-0602: PK parameters for tralokinumab after single and multiple intravenous dose

Parameter [a]	Tralokinumab IV dose group					
	Dose 1 (Week 0)			Dose 3 (Week 8)		
	1 mg/kg (N=8)	5 mg/kg (N=8)	10 mg/kg (N=3)	1 mg/kg (n=6)	5 mg/kg (n=7)	10 mg/kg (n=1)
AUC_{τ}, µg×day/mL	297 ± 42	1667 ± 303	3055 ± 719	463 ± 89[b]	2300 ± 350[b]	4593
$AUC_{0-\infty}$, µg×day/mL	421 ± 83	2282 ± 393	3825 ± 662	ND	ND	ND
C_{max}, µg/mL	29.9 ± 5.2	154 ± 35	305 ± 31	40.9 ± 4.8	177 ± 25	393
C_{28}, µg/mL	5.2 ± 1.3	26.7 ± 4.9	40.7 (n=1)	8.5 ± 2.0	38.7 ± 12.3	79.6
CL[c], mL/kg/day	2.41 ± 0.45	2.23 ± 0.46	2.64 ± 0.42	2.19 ± 0.42[b]	2.20 ± 0.39[b]	2.18
$t_{½}$, days	16.6 ± 2.7	16.1 ± 3.6	11.8 ±1.9	22.2 ± 2.2[b]	19.9 ± 3.1[b]	18.0
V_d, mL/kg	56.7 ± 8.0	51.0 ± 10.4	44.0 ± 0.8	ND	ND	ND
AR	ND	ND	ND	1.58 ± 0.21	1.39 ± 0.10	1.67

[a] AUC_{τ}, $AUC_{0-\infty}$, C_{max}, and C_{28} are given as geometric mean ± standard deviation (SD), and other parameters are given as arithmetic mean ± SD.

[b] Not included in statistical output; values derived from individual data provided in Appendix 16.1.13 Tables A1 (AUC_{τ} and CL) and A4 ($t_{½}$), combined with information from Listing 16.2.5.1 (dose group versus subject number).

[c] Value for dose 1 based on $AUC_{0-\infty}$, for dose 3 based on AUC_{0-28}.

Abbreviations: AR = accumulation ratio after 3 doses, 4 weeks apart, calculated as $AUC_{Day\ 56-84}/AUC_{Day\ 0-28}$; AUC = area under the serum concentration–time curve; AUC_{τ} = AUC over the dosing interval (Day 0–28 for dose 1, Day 56–84 for dose 3); $AUC_{0-\infty}$ = AUC from time zero extrapolated to infinity; C_{28} = observed serum concentration 28 days after each dose; CL = clearance (after IV dosing); C_{max} = maximum observed serum concentration after dosing; n = number of subjects with data; N = number of subjects in analysis set; ND = not determined; $t_{½}$ = terminal elimination half-life; V_d = apparent volume of distribution (after IV dosing).

Systemic exposure to tralokinumab, as assessed by C_{max} and AUC, appeared to increase in a dose-proportional manner across the dose range. There was no evidence of immunogenicity induced by tralokinumab in any subject.

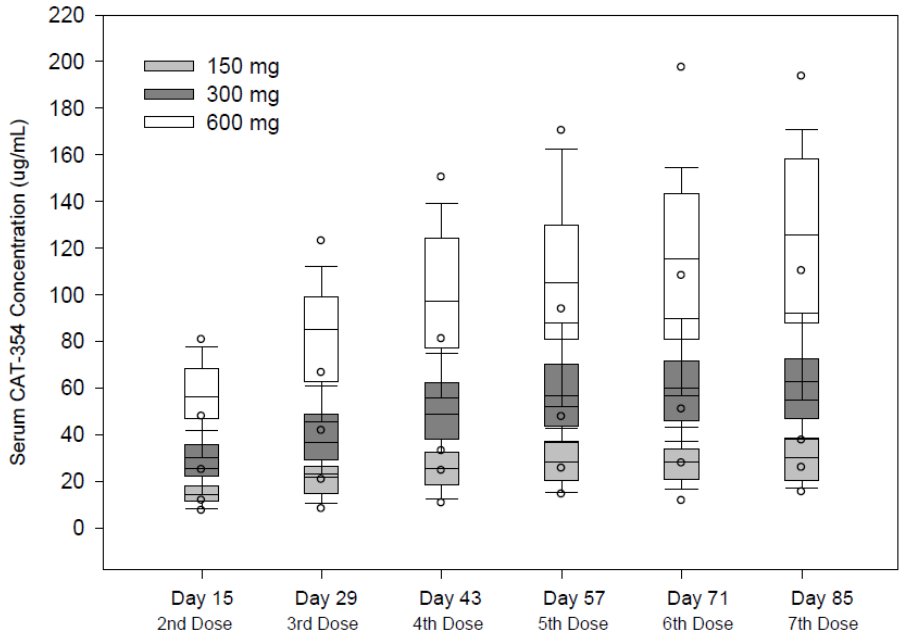


Figure 3 Trial MI-CP199: trough concentrations of tralokinumab after subcutaneous dosing (150, 300, or 600 mg) every 2 weeks for 12 weeks

Serum trough concentrations of tralokinumab increased in a dose-dependent manner, as shown in Figure 3. Within each dose group, the concentrations were comparable for the last 2 doses, indicating that steady state was reached. No evidence of immunogenicity was observed in any subject during the trial.

In study CD-RI-CAT-354-1049, at Week 13, the mean serum trough concentrations of tralokinumab were comparable in the 300 mg Q2W group (76.6 µg/mL) and the 300 mg Q2/4W group (66.2 µg/mL). After the switch at Week 13 from Q2W to Q4W in the Q2/4W group, the mean trough concentration at Week 25 in this group was approximately half (32.3 µg/mL) that at Week 13, consistent with linear PK. Mean trough concentrations were comparable from Week 13 to Week 53 for the 300 mg Q2W group and from Week 25 to Week 53 for the 300 mg Q2/4W group, indicating that steady state was reached. Tralokinumab accumulated after multiple dosing, as assessed by trough concentrations; the ratio of mean trough concentrations at Week 13 versus Week 5 ranged from 1.40 to 1.58. Six subjects (2.0%) dosed with tralokinumab and 7 subjects (4.6%) dosed with placebo had confirmed post-dose ADA-positive samples. Antibody titres ranged from 1–5 in the subjects with ADA-positive samples in the tralokinumab groups. The observed presence of ADAs did not influence the PK of tralokinumab; this could be attributable to the low antibody titres or to a transient response.

Distribution

The volume of distribution of tralokinumab has been determined in 4 clinical trials (Table 6).

Table 6 Estimates of tralokinumab volume of distribution

Parameter[a]	Clinical trial, dosing (S_D=single dose; M_D=multiple dose)			
	CAT-354-0703, S_D	MI-CP224[b], S_D	CAT-354-0401, S_D	CAT-354-0602, M_D
V_d, mL/kg	63.6	ND	87.3–155	44.0–56.7
V/F, mL/kg	ND	91.1–105	ND	ND

V_d = apparent volume of distribution after IV dosing; V/F = apparent volume of distribution after SC dosing.

[a] Values are given as arithmetic means. In trials with >1 dose group (with different values), the means for each dose group are given as a range.

[b] Trial conducted in Japanese population.

Based on the final popPK model, the volume of distribution at steady state was estimated to 4.2 L (V2 + V3) for a typical AD subject weighing 75 kg.

Elimination

The half-life (t½) and clearance (CL) of tralokinumab have been determined in 4 clinical trials (Table 7).

Table 7 Estimates of tralokinumab clearance and terminal half-life

Parameter[a]		Clinical trial, dosing (S_D=single dose; M_D=multiple dose)			
		CAT-354-0703, S_D	MI-CP224[b], S_D	CAT-354-0401, S_D	CAT-354-0602, M_D
CL, mL/kg/day		2.4	ND	2.6–3.7	2.2–2.6
CL/F, mL/kg/day		3.3–3.6	3.1–3.3	ND	ND
$t_{½}$, days	IV	21	ND	18–34	ND
	SC	19	20–25	ND	12–17 (first dose)[c] 18–22 (third dose)[d]

[a] Values are given as arithmetic means. In trials with >1 dose group (with different values), the means for each dose group are given as a range.

[b] Trial conducted in Japanese population.

[c] Determined over a period of approximately 4 weeks after the first dose (that is, <2 × $t_{½}$).

[d] Determined over a period of up to 13 weeks after the third and final dose.

Abbreviations: CL = clearance (after IV dosing); CL/F = apparent clearance (after SC dosing); IV = intravenous; ND = not determined; SC = subcutaneous; $t_{½}$ = terminal elimination half-life; V_d = apparent volume of distribution after IV dosing; V/F = apparent volume of distribution after SC dosing.

Based on the final popPK model, the estimated CL was 0.149 L/day and mean (SD) half-life was estimated to be 22 days for a typical AD subject weighing 75 kg. In phase 1 trials with IV dosing, clearance was estimated to be between 0.179 and 0.211 L/day.

No specific excretion or metabolism studies were conducted. As a monoclonal antibody, tralokinumab is not expected to undergo significant renal or hepatic elimination. Tralokinumab is expected to degrade to small peptides and individual amino acids.

Dose proportionality and time dependencies

The PK of tralokinumab was found to be linear, with a dose-proportional increase in drug exposure between 45 mg and 600 mg. After administration of a loading dose of 600 mg and subsequent 300 mg Q2W of tralokinumab steady state was reached after 16 weeks of treatment. The trough concentration at Week 16 ranged from 81 and 91 µg/mL. Tralokinumab accumulated after multiple dosing, as

assessed by trough concentrations; the accumulation factor is approximately 1.5 fold. A dosing regimen of 300 mg Q4W resulted in a mean trough concentration of approximately half of that observed for the 300 mg Q2W regimen. This is consistent with the simulations based on the popPK model and is consistent with linear PK.

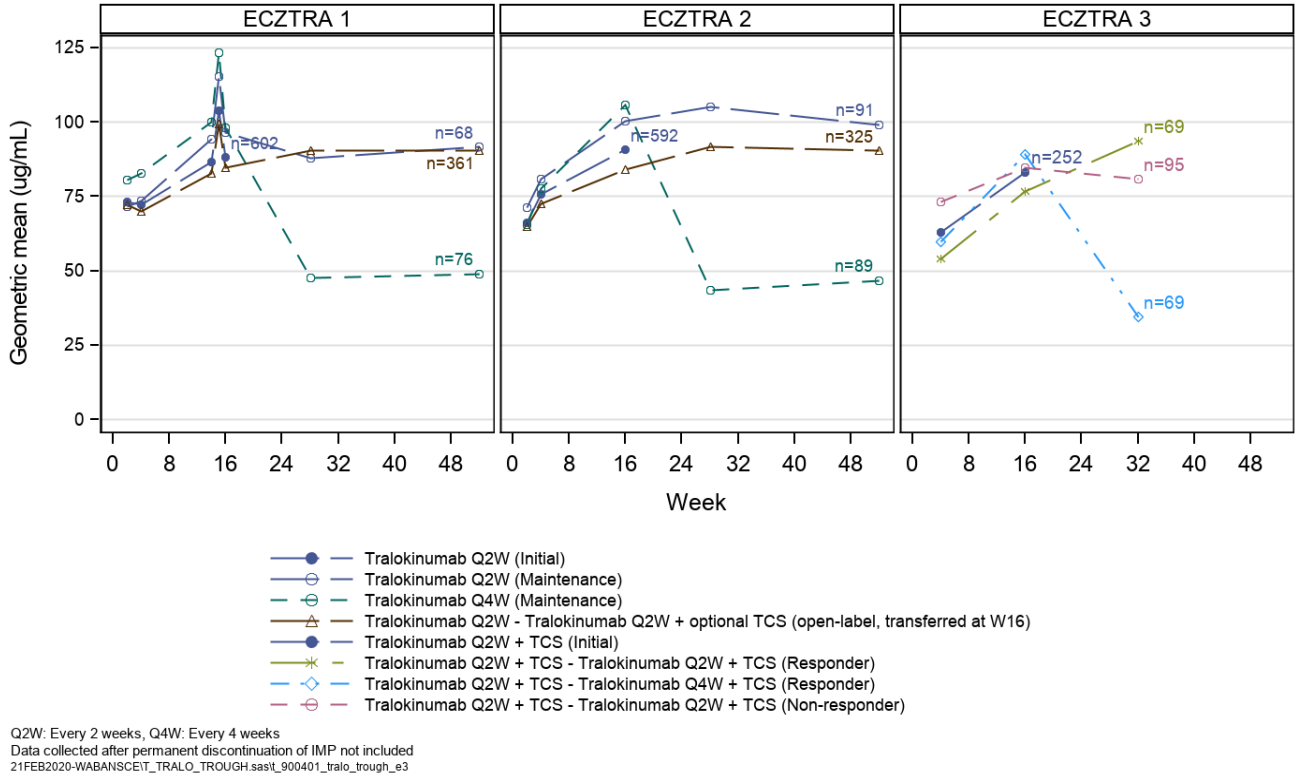


Figure 4 ECZTRA 1, 2, and 3: mean serum concentrations of tralokinumab after subcutaneous dosing (300 mg) every 2 or 4 weeks for up to 52 weeks

Intra- and inter-individual variability

Based on the C_{trough} values at steady state (Weeks 14 and 16) in the phase 3 mono therapy trials (ECZTRA 1 and 2), the intra-subject variability (CV%) was estimated to 23.4%. This is in accordance with the proportional residual error estimated in the popPK model (CV% = 21.6%).

In the population PK analysis, the estimated inter-individual variabilities of clearance (CL) and volume of the central compartment (V2) were moderate, with a CV% of 31.3% for CL and 40.1% for V2. In the ECZTRA 1 trial, inter-individual variability in trough concentrations at Week 16 was moderate to high (CV 66.1%).

Integrated analysis of immunogenicity

For the integrated analysis of immunogenicity in AD, the anti-drug antibodies (ADA) ECZTRA analysis set was applied including data from all subjects treated in the ECZTRA 1, 2, 3, and 5 trials.

Incidence of ADA

In ECZTRA 1, ECZTRA 2, ECZTRA 3, and the vaccine-response study, the incidence of ADA up to 16 weeks was 1.4% for patients treated with tralokinumab and 1.3% for patients treated with placebo.

Among the 1939 subjects treated with tralokinumab at any time point, 84 (4.3%) subjects had treatment-emergent ADA and 2 (0.1%) subjects had treatment-boosted ADA. Thus, the ADA incidence for the entire trial period was 4.6% among tralokinumab-treated subjects. For 14 (0.9%) of these subjects, the response was persistent. Among the 629 tralokinumab-naïve subjects, 9 (1.4%) subjects had treatment-emergent ADA and none had treatment-boosted ADA. For all subjects in the ADA ECZTRA analysis set with positive ADA status, ADA titres were generally low, ranging from <10–640.

There was no obvious pattern in the development of ADA across the different trial periods. Furthermore, there was no indication of increased development of ADA upon re-treatment, that is, after initial treatment with tralokinumab, maintenance treatment with placebo, and subsequent transfer to open-label treatment with tralokinumab.

Incidence of neutralising antibodies (NAb)

18 (1%) of the 1939 tralokinumab-treated subjects and 3 (0.5%) of the 629 tralokinumab-naïve subjects in the ADA ECZTRA analysis set were positive for NAb. For all of the 18 tralokinumab-treated subjects positive for NAb, the response was treatment-emergent.

Special populations

Impaired renal and hepatic function

No clinical trials have been conducted to evaluate the effect of renal or hepatic impairment on the PK of tralokinumab. As a monoclonal antibody, tralokinumab is not expected to undergo significant renal or hepatic elimination.

In the popPK analysis, mild or moderate renal impairment (eGFR of 30–89 mL/min) was not found to have a clinically relevant effect on tralokinumab exposure. Very limited data were available in subjects with severe renal impairment (only 1 subject included in the popPK analysis). Mild hepatic impairment was not found to affect the PK of tralokinumab. Very limited data were available in subjects with moderate or severe hepatic impairment (9 subjects included in the popPK analysis).

Gender, race and age

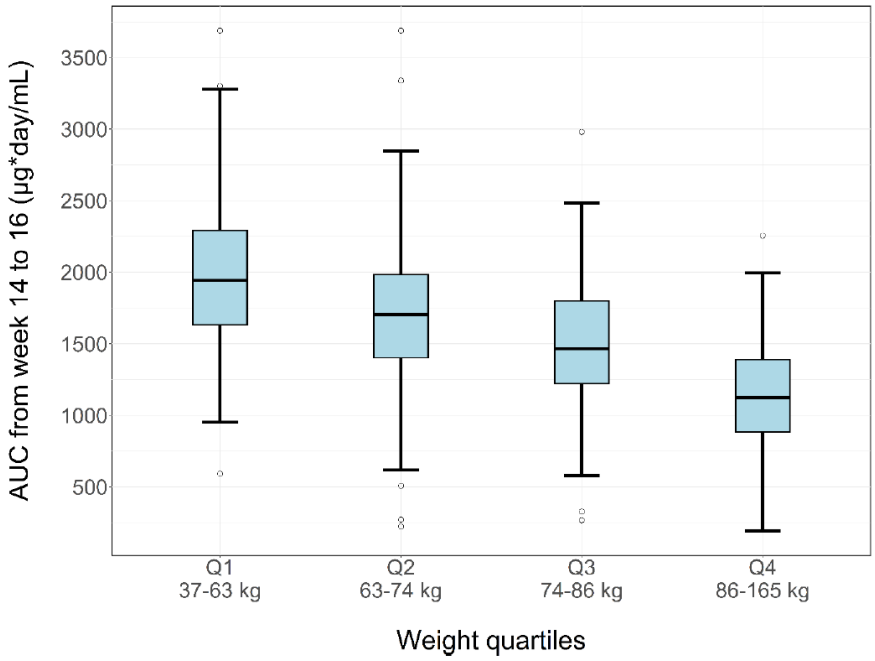
In the popPK analysis, sex, race and age were not found to have a clinically relevant effect on tralokinumab exposure. Clinical studies included subjects aged from 18 to 92 years, and 131 subjects in the popPK analysis were ≥65 years of age.

Table 8 Subjects include in popPK model by age

	Age ≤64	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
popPK model	2430	112	17	2

Body weight

The popPK analysis identified body weight as a statistically significant and clinically relevant covariate affecting clearance and volume parameters. Using the final popPK model, simulations were conducted for all subjects in the ECZTRA trials to evaluate the effect of body weight on tralokinumab exposure ($AUC_{Week\ 14\text{-}16}$). As shown in Figure 5, there is a clear correlation between exposure and body weight. The difference between the predicted median exposure of Q1 [1941 µg.day/mL] and Q4 [1125 µg.day/mL]) was <2-fold.



Notes: Boxplot depicting the correlation between individually predicted area under the serum concentration–time curve from Week 14–16 ($AUC_{Week\ 14\text{-}16}$) for all subjects in ECZTRA trials, grouped by weight quartiles. Only subjects who received 6 or more doses of tralokinumab during the first 119 days and had a PK sample in the time interval 105–119 days were included in the plot.

Figure 5 Final model: $AUC_{week14\text{-}16}$ versus weight quartiles in ECZTRA trials

Pharmacokinetic interaction studies

No formal PK drug interaction studies were conducted with tralokinumab. It is not expected that tralokinumab will directly interact with other drugs. However, since AD is associated with elevated pro-inflammatory cytokines, and increased levels of certain cytokines during chronic inflammation can alter the formation of cytochrome P450 (CYP) enzymes, there is potential for a disease-drug interaction. This potential interaction is elucidated in an ongoing clinical trial in AD patients (LP0162-1342).

2.4.3. Pharmacodynamics

Mechanism of action

Tralokinumab is a monoclonal antibody of the IgG4 subclass that specifically neutralises the IL-13 cytokine by inhibiting the interactions with the IL-13 receptors (IL-13Rα1 and IL-13Rα2). IL-13 is an immunoregulatory cytokine that plays an important role in the pathogenesis of AD.

Primary pharmacology

The tralokinumab biomarker programme in subjects with AD was aimed at investigating the mode of action of tralokinumab in skin and blood. The programme included exploratory analyses of molecular, cellular, and microbial markers in serum or skin that are related to AD or to the activity of tralokinumab in subjects with AD. The phase 3 trial ECZTRA 1 was pivotal to these analyses and provided most of the data. The phase 2b dose-finding trial D2213C00001 provided supportive data. In addition, the phase 3 trials ECZTRA 2 and 3, along with the phase 2 trial ECZTRA 5, provided data for 2 of the serum biomarkers (IgE and lactate dehydrogenase (LDH)).

Serum biomarkers

In the phase 2b dose-finding trial D2213C00001 as well as in the pivotal phase 3 trial ECZTRA 1, subjects receiving tralokinumab Q2W had reduced levels of the Th2-related serum biomarkers chemokine ligand 17 (CCL17) and periostin already from Week 4, with further reductions at Week 12 or Week 16. Dipeptidyl peptidase 4 (DPP4) was only minimally affected, with an increase in the median serum concentration at Week 12 or Week 16 compared with baseline.

Across the phase 2b and pivotal phase 3 trials, serum levels of IgE were reduced at Week 12 in subjects receiving tralokinumab compared with subjects receiving placebo, whereas lactic acid dehydrogenase (LDH) levels were only marginally reduced. A similar pattern for IgE and LDH was observed in ECZTRA 5.

The results for the serum biomarkers that were measured in at least 2 of the phase 2b and pivotal phase 3 trials in AD are summarised in Table 9.

Table 9 Comparison of serum biomarkers across phase 2b and phase 3 trials in AD: ratio of tralokinumab 300 mg to placebo (change from baseline up to end-of-treatment)

Serum biomarker [a]	Visit	Phase 2b trial	Pivotal phase 3 trials		
		D2213C00001 (N=103)	ECZTRA 1 (N=798)	ECZTRA 2 (N=792)	ECZTRA 3 (N=378)
Periostin	Week 4	0.79	0.83	–	–
	Week 12/16[b]	0.66	0.79	–	–
CCL17	Week 4	0.49	0.60	–	–
	Week 12/16[b]	0.41	0.42	–	–
DPP4	Week 4	0.98	0.94	–	–
	Week 12/16[b]	1.00	1.03	–	–
IgE[c]	Week 4	–	0.89	1.00	0.90
	Week 12	0.73	0.78	0.92	0.82
	Week 16	–	0.66	0.91	0.80
LDH	Week 4	–	0.93	0.92	1.03
	Week 12	–	0.91	0.94	0.95
	Week 16	–	0.92	0.94	0.95

Note: Data only shown for the Q2W (every 2 weeks) dosing regimen.

[a] Values given as the ratio of tralokinumab to placebo, based on tralokinumab and placebo values given as the mean ratio to baseline except for the IgE data - see note [c].

[b] Week 12 (end-of-treatment) in D2213C00001 and Week 16 (end of initial treatment period) in ECZTRA 1.

[c] Ratio based on tralokinumab and placebo values given as median change from baseline.

Abbreviations: CCL17 = C-C motif chemokine ligand 17 (also known as thymus- and activation-regulated chemokine, TARC); DPP4 = dipeptidyl peptidase 4; IgE = immunoglobulin E; LDH = lactate dehydrogenase; N = number of subjects in analysis set; '–' = data not collected.

Skin colonisation with *S. aureus*

Skin colonisation with *S. aureus* was assessed in the phase 2b dose-finding trial D2213C00001 as well as in ECZTRA 1. The pattern of results was consistent across the 2 trials: *S. aureus* colonisation was significantly reduced at Week 12 (D2213C00001) and Week 16 (ECZTRA 1) in subjects receiving tralokinumab compared with subjects receiving placebo.

Secondary pharmacology

No secondary clinical pharmacology studies were performed with tralokinumab. Please see the non-clinical section.

Pharmacodynamic interactions with other medicinal products or substances

The PD interactions between tralokinumab and two vaccines was assessed in Study LP0162-1341 (ECZTRA 5): a phase 2, randomised, double-blind, placebo-controlled trial in subjects with moderate-to-severe AD. The primary objective of this trial was to demonstrate non-inferiority of tralokinumab versus placebo with respect to immune responses to concomitantly administered vaccines based on a pre-specified non-inferiority limit of 25%. The trial assessed immunisation responses against 2 non-live vaccines, a combined Tdap (tetanus, diphtheria, pertussis) vaccine and a meningococcal vaccine.

Subjects were randomised in a 1:1 ratio to tralokinumab 300 mg or placebo Q2W (administered SC) for 16 weeks, following an initial loading dose (tralokinumab 600 mg or placebo). At Week 12, subjects received 1 dose of each vaccine before the administration of tralokinumab or placebo.

The percentage of subjects achieving each of the primary endpoints, positive anti-tetanus response and positive anti-meningococcal response at Week 16, was similar in the tralokinumab group and the placebo group (Table 10). For the estimated difference in response rate, the lower limit of the 95% CI was greater than the pre-specified non-inferiority margin of -25%, demonstrating non-inferiority of tralokinumab versus placebo with respect to immune responses to concomitantly administered, non-live vaccines.

Table 10 Positive vaccine response at Week 16: per protocol analysis set

Vaccine response at Week 16	Tralokinumab Q2W (n= 88) Responders (%)[1]	Placebo (n= 78) Responders (%)[1]	Difference in percentage[2] (95% CI)
Anti-tetanus response			
Anti-tetanus response	79/ 86 (91.9)	73/ 76 (96.1)	-4.2(-11.4,3.1)
Anti-meningococcal response			
Anti-meningococcal response	74/ 86 (86.0)	64/ 76 (84.2)	1.8(-9.2,12.8)
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1) Responders/total.

2) Mantel-Haenszel risk difference, stratified by baseline IGA.

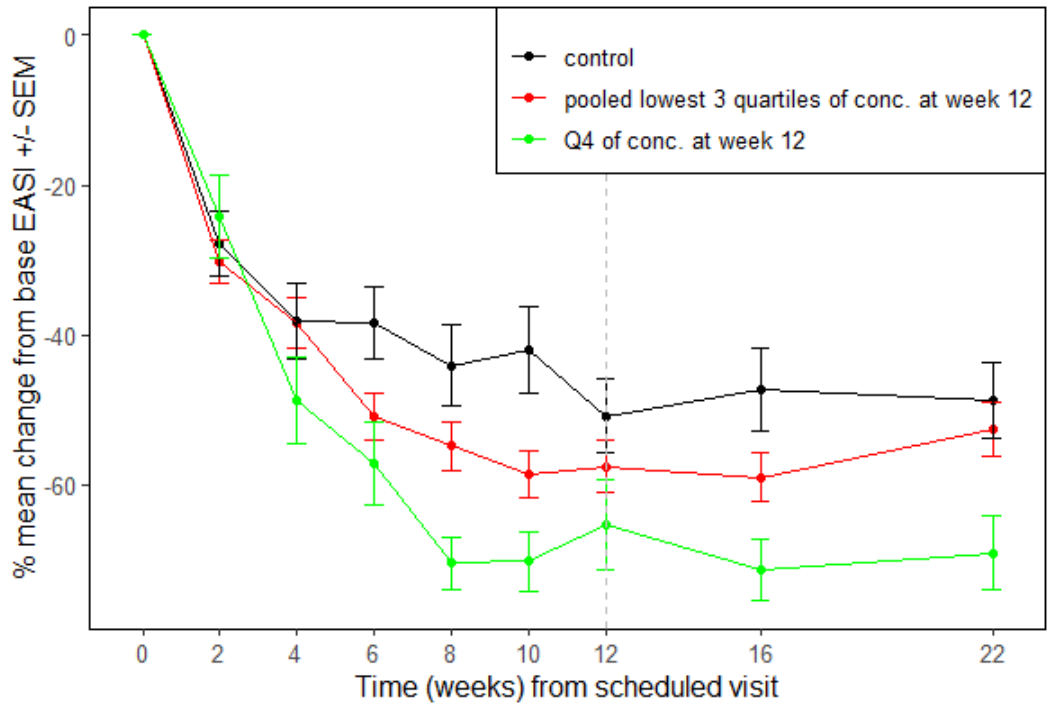
Abbreviations: CI = confidence interval; IGA = Investigator's Global Assessment; Q2W = every 2 weeks.

Relationship between plasma concentration and effect

Exposure-response analysis (phase 2b study D2213C00001)

The phase 2b trial D2213C00001 evaluated 3 doses of tralokinumab versus placebo, administered SC with concomitant use of TCS in adults with moderate-to-severe AD. The doses were 45 mg, 150 mg, and 300 mg (Q2W).

Individual Eczema Area and Severity Index (EASI) scores were stratified by individual tralokinumab serum concentration quartiles. As shown in Figure 6 subjects within the 75th exposure percentile (Q4) had best efficacy scores at Week 12. The trough concentration threshold characterising this subgroup of subjects with the highest exposure was 59.2 mg/L tralokinumab. 70% of the subjects in this subgroup received 300 mg Q2W, and the remaining 30% received 150 mg Q2W; no subject receiving 45 mg Q2W reached the threshold for the subgroup.



Abbreviations: conc. = concentration; EASI = Eczema Area and Severity Index; Q4 = 75th exposure percentile; SEM = standard error of the mean.

Figure 6 Trial D2213C00001: EASI response from Week 0–22 stratified by tralokinumab trough concentrations at Week 12

Exposure-response analysis (phase 3 ECZTRA trials)

Exposure data and selected response data up to Week 16 were provided from the phase 3 trials ECZTRA 1 and 2 (monotherapy pool) and ECZTRA 3 (tralokinumab–TCS combination trial). A total of 963 subjects were included in the ECZTRA 1+2 exposure-response (ER) analysis dataset and 334 subjects were included in the ECZTRA 3 ER analysis dataset.

Exposure-efficacy quartile analysis

The number of subjects per quartile and the quartile ranges for ECZTRA 1 + 2 are provided in Table 11.

Table 11 ECZTRA 1+2: Number of subjects stratified and quartiles by exposure variable and body weight

Quartile (Q)	N, C_{trough} (µg/mL, range)		N, AUC (µg×day/mL, range)		N, Body weight (kg, range)	
Placebo	194	-	194	-	-	-
Q1	193	2.8–72	193	1,613–9,347	193	37–63
Q2	192	72.2–98.7	192	9,365–11,586	192	63–73
Q3	192	98.9–127	192	11,599–13,908	192	73–84
Q4	192	127–340	192	13,925–25,861	192	84–165

Abbreviations: AUC = area under the serum concentration–time curve from time zero to Week 16 (individually predicted based on population pharmacokinetic modelling); C_{trough} = observed trough concentration at Week 16; EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment.

A clear relationship was observed between exposure (C_{trough} and AUC) and efficacy (EASI and IGA response). At Week 16, the subjects within the lowest exposure quartile (Q1) had the lowest response, and the subjects within the highest exposure quartile had the highest response (Table 12).

Table 12 ECZTRA 1+2: EASI and IGA responses at week 16 stratified by quartiles of body weight, model-predicted AUC, and tralokinumab trough concentration

Quartile (Q)	EASI (mean % change from baseline)			IGA 0/1 responders (%)		
	Quartile by body weight	Quartile by AUC	Quartile by C_{trough}	Quartile by body weight	Quartile by AUC	Quartile by C_{trough}
Q1	-65.7	-55.3	-53.5	34.2	22.5	20.3
Q2	-61.9	-62.9	-61.3	28.9	29.2	27.7
Q3	-59.1	-64.1	-64.8	29.3	30.9	30.9
Q4	-59.9	-64.4	-67.1	25	34.9	38.5
Q4-Q1	5.8	-9.1	-13.6	-9.2	12.4	18.2
Q3-Q1	6.6	-8.8	-11.3	-4.9	8.4	10.6

Notes: IGA 0/1 responders are defined as subjects with an IGA score of 0 (clear) or 1 (almost clear); number of subjects per quartile as well as quartile intervals are given in Panel 12.

Abbreviations: AUC = (individually predicted) area under the serum concentration–time curve from time zero to Week 16 visit; C_{trough} = observed trough concentration at Week 16; EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment.

Stratification of individual ΔEASI% by body weight showed that subjects in the lowest body weight quartile had a modestly improved efficacy response compared with subjects in the highest body weight quartile (ΔEASI% at Week 16: 5.8). However, the difference in ΔEASI% at Week 16 between the lowest and highest quartile was less pronounced for body weight than for AUC (-9.1) and C_{trough} (-13.6).

In the quartile analysis of ECZTRA 3, which included concomitant TCS treatment, the relationship between tralokinumab exposure and reduction in EASI score was consistent with the monotherapy pool (Table 13).

Table 13 ECZTRA 3: EASI and IGA responses at week 16 stratified by quartiles of observed body weight, model-predicted AUC, and tralokinumab trough concentration

Quartile (Q)	EASI (mean % change from baseline)		
	Quartile by C_{trough}	Quartile by AUC	Quartile by body weight
Q1	-72.0	-73.6	-74.4
Q2	-70.9	-66.3	-74.8
Q3	-72.9	-76.0	-76.3
Q4	-77.1	-76.9	-67.4
Q4-Q1	-5.1	-3.3	7.0
Q3-Q1	-0.9	-2.4	-1.9

Note: Number of subjects per quartile as well as quartile ranges are given in Panel 13.

Abbreviations: AUC = (individually predicted) area under the serum concentration–time curve from time zero to Week 16; C_{trough} = observed trough concentration at Week 16; EASI = Eczema Area and Severity Index.

Exposure-efficacy model analysis

The analysis dataset contained 1482 data pairs (C_{trough}, ΔEASI%) and 963 data pairs (AUC, ΔEASI%) from 963 subjects.

An E_{max} (estimated maximum effect) model was found to provide the best description of the relationship between efficacy and steady state exposure metrics. Race (Black or African American (BAA)/non-BAA) was found to have a significant effect on the E0, consistent with a higher placebo response in the BAA population than in non-BAA populations. Baseline EASI score was also found to have a significant effect on EC50, predicting that subjects with severe AD will have a lower level of response at the same exposure level compared with subjects with less severe AD.

The parameter estimates for the final model for the C_{trough} metric are shown in Table 14. The visual predictive check (VPC) for the final C_{trough} model is shown in Table 15. For the typical subject (non-BAA and baseline EASI score of 25), the steady state C_{trough} exposure estimated to achieve half of maximum treatment response was 37.8 µg/mL.

Table 14 ECZTRA 1+2: Final ER model parameters for percent change from baseline in EASI score versus trough concentration at steady state

Parameter [population]	Unit	Parameter estimate (RSE%)[a] [shrinkage%]
E_0 [All but BAA]	ΔEASI%	-31.4 (9)
EC_{50} [All but BAA]	µg/mL	37.8 (14)
E_{max} [All]	ΔEASI%	-88.9 (1)
Covariate		
E_0 ~ BAA[b] [BAA]	unitless	0.951 (26)
EC_{50} ~ Baseline EASI score[c] [All]	unitless	0.998 (24)
Inter-individual variability (IIV)		
IIV on E_0 (SD) [All]	ΔEASI%	39.7 (4) [30]
IIV on EC_{50} (CV%) [All]	CV%	205 (11) [45]
Correlation (E_0, EC_{50}) [All]	unitless	0.20
Residual error		
Additive [All]	ΔEASI%	13.1 (3) [27]

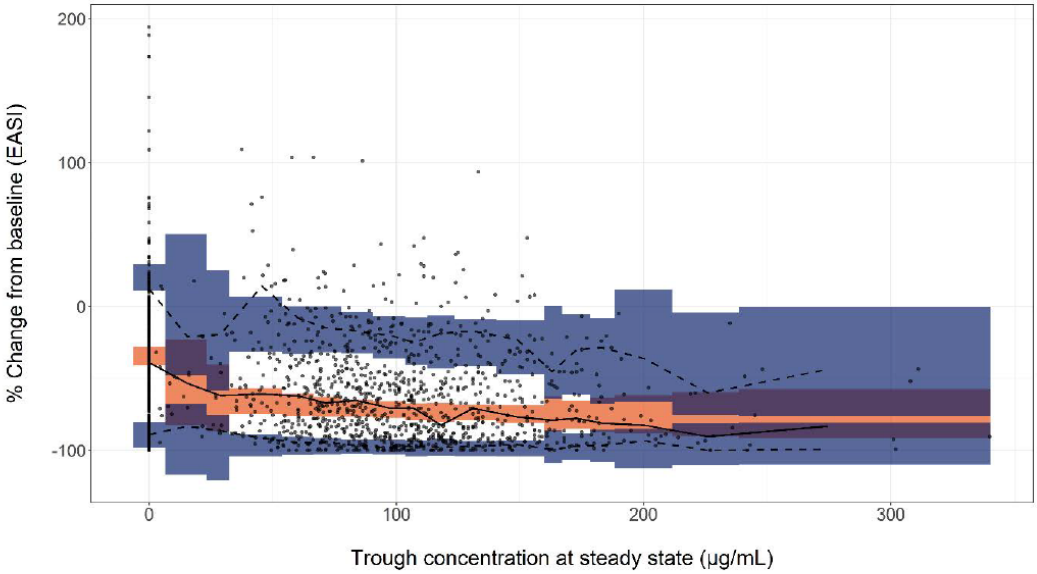
[a] RSE was obtained from the COVARIANCE option in NONMEM. For IIV, the RSE was calculated using the equation: $RSE\omega_{i,i} = 1/2 \times RSE\omega^2_{i,i}$. applicable for calculating RSE of a square root transformation.

[b] Effect of race on E_0 was implemented as: $E_0 = TV_{E0} \times (1+\theta)$, where TV_{E0} is the typical value of E_0 and θ is the covariate parameter.

[c] Baseline EASI score (bEASI) on EC_{50} was implemented as: $EC_{50} = TV_{EC50} \times (bEASI/25)^{\theta}$, where TV_{EC50} is the typical value of EC_{50} and θ is the covariate parameter.

Abbreviations: BAA = Black or African American; CV = coefficient of variation; E_0 = placebo response; E_{max} = maximum response; EC_{50} = trough concentration resulting in half maximal treatment response; EASI = Eczema Area and Severity Index; ΔEASI% = percent change from baseline in EASI score; IIV = inter-individual variability; RSE = relative standard error; SD = standard deviation.

Table 15 ECZTRA 1+2: Visual predictive check for final C_{trough} model



Notes: Data shown for steady state ΔEASI% versus C_{trough} (Weeks 14 and 16) in ECZTRA 1 and 2: Observed ΔEASI% (dots), median of observed ΔEASI% (solid line), 95% confidence interval of simulated median (orange shaded area), 95% confidence interval of simulated lower 5th and upper 95th percentiles (blue shaded areas), and observed 5th and 95th percentiles (dashed line).

Abbreviations: C_{trough} = trough concentration; EASI = Eczema Area and Severity Index; ΔEASI% = percent change from baseline in EASI score.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

The bioanalytical methods used to measure the serum concentration of tralokinumab (direct ELISA method and sandwich immunoassay) were considered sufficiently validated by CHMP.

No incurred samples reanalysis was performed at MedImmune which is accepted given that the same method was applied at LGC Ltd. and Covance and taking into account the acceptable method validation/assay performance at MedImmune. It has been confirmed that appropriate assay acceptance criteria were in place for routine analytical runs and that acceptable reference standards (clinical batches) were used during method validation. With respect to the query raised regarding the robustness of the assay performance at one of the laboratories (Covance Ltd.), it has been clarified that these run failures related to lab technician error.

The ADA and NAb assays were also adequate. CHMP noted the low number of samples with tralokinumab levels above the assay tolerance but considered that they would not have any material impact on the immunogenicity conclusions. The popPK analysis used for model development and evaluation was also considered acceptable.

Absorption - Bioavailability

PK data has been presented across 6 trials in healthy volunteers (2) and asthma patients (4), for a variety of doses and posology. Tralokinumab was administered in a similar way to the proposed AD dosing (i.e. 300mg every Q2W) in 2 asthma studies (MI-CP199 and CD-RI-CAT-354-1049).

Steady state PK data (week 13 to 53) for CD-RI-CAT-354-1049 demonstrated mean C_{min} values of 71.3 to 78.4 µg/mL while for MI-CP199 the highest mean C_{min} value was 86.8 µg/mL at week 13. These results are slightly lower than the C_{trough} mean of 99.9 µg/mL from the pivotal phase 3 ECZTRA 1 trial in AD. For healthy volunteer studies CAT-354-0703 and MI-CP224, tralokinumab was administered as a single 300mg SC dose. $AUC_{0\text{-}inf}$ values were 1030 and 1459 µg×day/mL and C_{max} values were 34.4 and 44.8 µg/mL.

The absolute bioavailability of tralokinumab following SC dosing was estimated by popPK analysis to be 76%. In the healthy volunteer study CAT-354-0703, the bioavailability was estimated to be 62% for the 150 mg dose and 60% for the 300 mg dose following SC administration.

The applicant considered the trial results underestimated the SC bioavailability due to differences and variability in the body weight across the different treatment arms. This could be plausible given that the popPK analysis identified body weight as a statistically significant and clinically relevant covariate.

Distribution

The volume of distribution was estimated across 4 PK trials in healthy volunteers and asthma patients. In these trials, the volume of distribution, Vd, ranged from 44 to 155 mL/kg.

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

The relatively small volume of distribution for tralokinumab is typical of monoclonal antibodies, which are largely confined to the vascular and interstitial spaces due to their large molecular size and poor lipophilicity.

Elimination

CL and $t_{1/2}$ were estimated across 4 PK trials in healthy volunteers and asthma patients. In these trials, CL ranged from 2.2 to 3.7 mL/kg/day. $T_{1/2}$ ranged from 18 to 34 days, excluding the $t_{1/2}$ determined following the first dose in the CAT-354-0602 trial.

In ECZTRA 1, ECZTRA 2, and ECZTRA 3*,* clearance was estimated by population PK analysis to be 0.149 L/day. In phase 1 trials with IV dosing, clearance was estimated to be between 0.179 and 0.211 L/day.

Half-life is 22 days, consistent with the typical estimate for human IgG4 monoclonal antibodies targeting soluble cytokines.

The lack of specific excretion or metabolism studies is acceptable because tralokinumab is a protein which is primarily cleared by proteolytic catabolism and broken down into small peptides and individual amino acids.

Dose proportionality and time dependency

Data from study MI-CP224 suggests dose proportionality for C_{max} and AUC for flat doses, SC, between 150mg and 600mg. In contrast, data from study 354-0401 indicates C_{max} estimates increased supra-proportionally across all doses tested from 0.1 to 30 mg/kg, while AUC estimates increased supra-proportionally from 10 to 30 mg/kg.

Dose proportionality from other studies listed above was not discussed or analysed in detail. In addition, only 5 patients were tested at 30mg/kg throughout the whole clinical development programme.

Therefore, the statement on linearity in section 5.2 of the SmPC stating that '*Exposure of tralokinumab increases proportionally to the dose of tralokinumab between 150-600 mg*' is based on the phase 1 MI-CP224 study.

The data support absence of time-dependent behaviour.

Pharmacokinetics in the target population

In the phase 2b study (D2213C00001), tralokinumab trough concentrations at steady state in subjects with AD were comparable with those observed in previous asthma studies.

Consistent across the pivotal phase 3 studies (ECZTRA 1, 2 and 3) and the phase 2 ECZTRA 5 study, tralokinumab trough concentrations at Week 2 and/or Week 4 were close to the steady-state concentration at Week 16, which supports the use of a loading dose. Across clinical studies (ECZTRA 1, ECZTRA 2 and ECZTRA 3), the mean ±SD steady-state trough concentration ranged from 98.0±41.1 mcg/mL to 101.4±42.7 mcg/mL for 300 mg dose administered every other week.

The mean trough concentration of tralokinumab following a switch from Q2W to Q4W reduced by approximately half, suggesting linear PK.

Integrated analysis of immunogenicity

Clinical data from the trials with tralokinumab in AD showed that the rate of ADA was low. There was generally no impact of ADA/NAb on PK or efficacy. However, the low number of ADA positive subjects limited the comparison between groups. No distinct pattern of AEs was found in the ADA/NAb positive subjects and no increased risk of anaphylaxis and serious allergic reactions, immune complex disease, serum sickness, or serum sickness-like reactions was identified in the ADA ECZTRA analysis set.

Special populations

It is agreed that renal impairment, hepatic impairment, gender or age are unlikely to affect the PK of tralokinumab and that a dose adjustment is not warranted.

In the popPK analysis, race (Black or African Americans, Asian and White and others) was found to be a statistically significant covariate on both CL and V2. Ethnicity was found to be a statistically significant covariate on CL. However, for both race and ethnicity, the effect on the CL or V2 was low and deemed not clinically relevant. Thus, no dose adjustment is warranted in terms of race.

In the popPK analysis, the effect of body weight was statistically significant and clinically relevant covariate affecting CL and volume parameters. This effect results in decreasing steady-state exposure of tralokinumab with increasing body weight. However, simulations based on the population PK/PD model suggested that an increase in dose to QW for subjects with high body weight may result in only a small increase in treatment response. Furthermore, in the quartile exposure-safety analyses for conjunctivitis and respiratory tract infections, no significant trends were observed, and an exposure limit related to safety could not be identified. Therefore, flat dosing of tralokinumab for the Q2W regimen, irrespective of weight, is considered acceptable.

Despite exposure being reduced by around half, the applicant contends that the Q4W regimen is adequate to maintain efficacy in subjects who achieved a clinical response at Week 16. It is acknowledged that maintenance treatment was not part of the exposure-response analysis and that the exposure-response relationship cannot be transferred to this situation. However, the reduced exposure in patients with a high body weight (>100 kg), coupled with the reduced exposure with the Q4W regimen, suggests that the Q4W regimen may not be appropriate for patients with a high body weight. This information has been included in section 4.2 of the SmPC.

Interactions

No formal PK drug interaction studies were conducted with tralokinumab which was considered acceptable by CHMP (please see section PK 'interactions' section).

Pharmacodynamics

Primary pharmacology – biomarker analyses

The exploratory biomarker analysis of the phase 2b study D2213C00001 showed an effect of tralokinumab on selected biomarkers and suggested a greater effect of the 300 mg Q2W dose compared to lower doses.

The biomarker sub study of the phase 3 ECZTRA 1 trial (LP0162-1325) underlines the importance of IL-13 in the pathophysiology of AD and the effects of treating with tralokinumab. By analysing serum and skin samples it was shown that IL-13 expression correlates with other inflammatory markers, skin colonisation with *S. aureus* and clinical disease severity.

Across the pivotal phase 3 ECZTRA trials, serum levels of biomarkers known to be upregulated in patients with AD and to respond to treatment were shown to be reduced with tralokinumab therapy. Skin biomarkers associated with epidermal hyperplasia were reduced and those associated with barrier integrity were increased with tralokinumab treatment. Treatment with tralokinumab also reduced the abundance of *S. aureus* in lesional skin, which correlates with a reduction in disease severity of AD.

Overall, the findings of the biomarker analyses confirm the mode of action of tralokinumab and provide support for the efficacy of this drug in improving disease symptoms in patients with AD.

Pharmacodynamic interactions

The phase 2 ECZTRA 5 trial demonstrated non-inferiority of tralokinumab versus placebo with respect to immune responses to Tdap and meningococcal vaccines, based on the predefined non-inferiority margin of -25%. The results support that non-live vaccines are effective/immunogenic in adult patients with moderate-to-severe AD treated with tralokinumab. However, live and live attenuated vaccines should not be given concurrently with tralokinumab as clinical safety and efficacy have not been established.

Exposure-response analyses

The ER analysis of data from the phase 2b study (D2213C00001) showed a positive relationship between tralokinumab exposure and efficacy, with the highest trough concentration quartile (C_{trough} threshold >59 mg/L) showing superior efficacy over other quartiles and 70% of subjects in this quartile received 300 mg Q2W. These results support the selection of the 300 mg Q2W dose for the phase 3 development programme.

The ER analysis from the phase 3 ECZTRA trials showed a clear positive relationship between efficacy and tralokinumab exposure at steady state in both the quartile and model-based analysis of the ER data for the 300 mg Q2W. In the quartile exposure-safety analyses for conjunctivitis, there was a trend for higher C_{trough} levels and increased incidence of conjunctivitis, but this trend was not statistically significant.

In the ER model analysis, an E_{max} model provided the best fit to the data. All parameters included in the final model were estimated with reasonably good precision (all RSE <30%). Interindividual variability on E0 and EC50 was reduced in the final model compared to the base model but remained high, particularly for EC50 (IIV 205%). Diagnostic plots generally showed an adequate fit of the model to the data. The VPC showed that the predictive performance of the model was adequate. Of the covariates tested in the ER model analysis, race (BAA/non-BAA) and disease severity (baseline EASI score) were found to affect the ER relationship. The response of the BAA population in the placebo group was almost twice as big as the response in non-BAA populations. The trough concentration resulting in half maximal treatment response concentration was shown to increase with increasing EASI score at baseline. However, simulations based on a population PK/PD model suggested only a minor increase in the proportion of EASI-75 responders at Week 16 after increasing the dosing frequency to once weekly in subjects with severe AD.

2.4.5. Conclusions on clinical pharmacology

The PK profile of tralokinumab has been adequately characterised. Based on the PK-PD data presented in the dossier, the proposed posology of 600 mg (four 150 mg injections) followed by 300 mg (two 150 mg injections) administered every other week as SC injection is agreed. Appropriate information relevant for the prescribers and patients has been included in the SmPC and package leaflet accordingly.

2.5. Clinical efficacy

2.5.1. Dose response studies

The selection of the dose for further development in AD subjects was supported by the phase 2b randomised, double-blinded, placebo-controlled, dose-ranging study in adult subjects with moderate-to-severe AD (D2213C00001). This study assessed the efficacy of tralokinumab Q2W at doses of 45,

150 and 300 mg in terms of Investigator's Global Assessment (IGA) response rate and change in Eczema Area and Severity Index (EASI) score from baseline at week 12. No significant differences were evident between the 150 mg and 300 mg tralokinumab treatment groups.

2.5.2. Main studies

The clinical development programme consisted in 3 randomised phase 3 studies to evaluate the efficacy and safety of tralokinumab as monotherapy (ECZTRA 1, ECZTRA 2) or in combination with TCS (ECZTRA 3) in subjects with moderate-to-severe AD who are candidates for systemic therapy. In this assessment report, studies ECZTRA 1 and ECZTRA 2 are discussed together since they have an almost identical study design whereas ECZTRA 3 is discussed separately.

ECZTRA 1 and ECZTRA 2

Methods

Both studies were randomised, double-blind, placebo-controlled trial evaluating the efficacy and safety of tralokinumab monotherapy in adult subjects with moderate-to-severe AD who were candidates for systemic therapy.

The trials 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 and ADA (Figure 7).

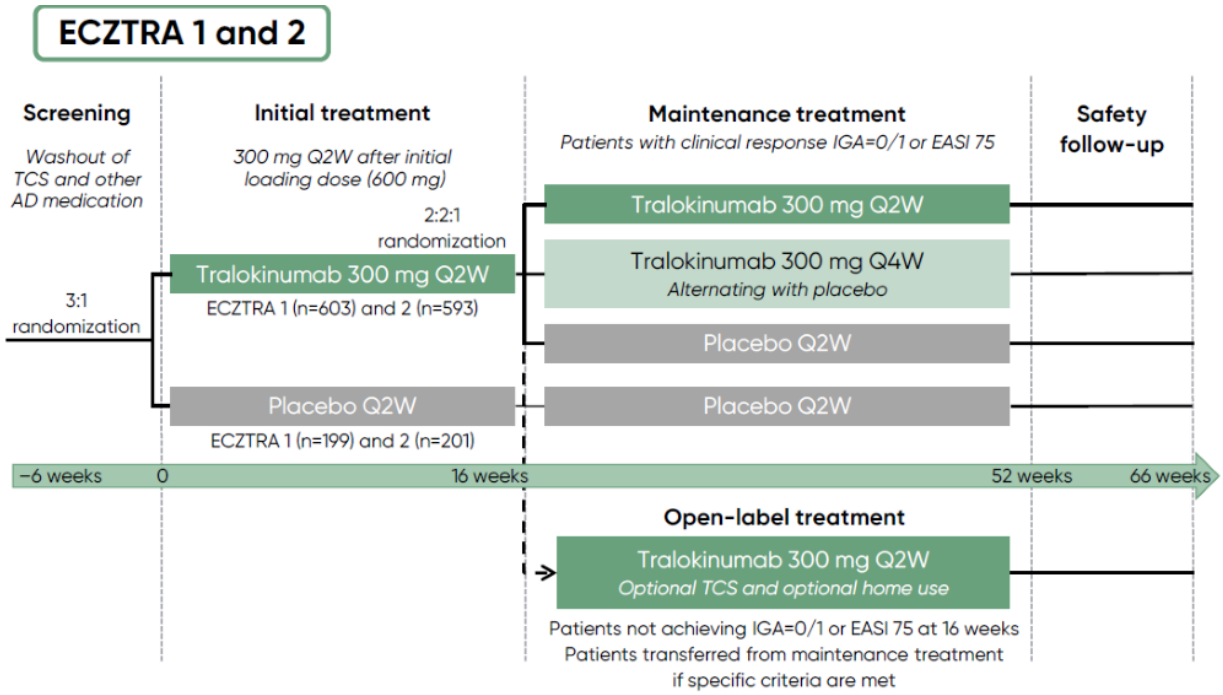


Figure 7 ECZTRA 1 and ECZTRA 2 clinical study design

Study Participants

Main inclusion criteria

- Age 18 and above;
- Diagnosis of AD as defined by the Hanifin and Rajka (1980) criteria for AD and for ≥1 year;
- Subjects who had a recent history (within 1 year before the screening visit) of inadequate response to treatment with topical medications or for whom topical treatments were otherwise medically inadvisable (e.g. due to important side effects or safety risks);
    - Inadequate response was defined as failure to achieve and maintain remission or a low disease activity state (comparable to IGA 0 = clear to 2 = mild) despite treatment with a daily regimen of TCS of medium to higher potency (±TCI as appropriate), applied for at least 28 days or for the maximum duration recommended by the product information (e.g. 14 days for super-potent TCS), whichever was shorter;
    - Subjects with documented systemic treatment for AD in the past year were also considered as inadequate responders to topical treatments and were potentially eligible for treatment with tralokinumab after appropriate wash-out;
    - Important side effects or safety risks were those that outweighed the potential treatment benefits and included intolerance to treatment, hypersensitivity reactions, significant skin atrophy, and systemic effects, as assessed by the investigator or by the subject's treating physician.
- AD involvement of ≥10% BSA at screening and baseline (Visit 3);
- An EASI score of ≥12 at screening and ≥16 at baseline;
- An Investigator's Global Assessment (IGA) score of ≥3 at screening and at baseline;
- A Worst Daily Pruritus Numerical Rating Scale (NRS) average score of ≥4 during the week prior to baseline;
    - Worst Daily Pruritus NRS at baseline was calculated from daily assessments of worst itch severity (Worst Daily Pruritus NRS) during the 7 days immediately preceding randomisation (Day -6 to 0). A minimum of 4 Worst Daily 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 for screening.
- Subjects were required to have applied a stable dose of emollient twice daily (or more, as needed) for at least 14 days before randomisation.

Main exclusion criteria

- Subjects with active dermatologic conditions that could confound the diagnosis of AD or would interfere with assessment of treatment, such as scabies, cutaneous lymphoma, or psoriasis;
- Subjects with known active allergic or irritant contact dermatitis that was likely to interfere with the assessment of severity of AD or with a history of any active skin infection within 1 week prior to randomisation;
- Subjects with history of clinically significant infection, defined as systemic infections or serious skin infection requiring parenteral medication within 4 weeks prior to enrolment;
- Subjects with known immunodeficiency disorder or receiving immunosuppressive medication and subjects with a positive hepatitis B or C;

- Subjects with previous immune complex disorders;
- Subjects who had a history of attempted suicide or were considered at significant risk of committing suicide.

Treatments

Investigational treatment

All randomised subjects received a loading dose of 600 mg on Day 0 (baseline): 4 SC injections (each 1.0 mL) of 150 mg tralokinumab or placebo.

At subsequent visits in the initial treatment period, each subject received 2 SC injections (each 1.0 mL) of 150 mg tralokinumab Q2W or placebo Q2W to receive a total dose of 300 mg tralokinumab or placebo.

Tralokinumab responders were re-randomised to an additional 36-week blinded maintenance treatment with:

- Tralokinumab Q2W (2 SC injections [each 1.0 mL] of 150 mg tralokinumab);
- Tralokinumab Q4W (alternating dose administrations: 2 SC injections [each 1.0 mL] of 150 mg tralokinumab and 2 SC injections [each 1.0 mL] of placebo);
- Placebo Q2W (2 SC injections [each 1.0 mL] of placebo).

Subjects (i.e. non-responders at week 16 or during the maintenance phase) who had been transferred to open-label treatment received 2 SC injections (each 1.0 mL) of 150 mg tralokinumab Q2W.

Background treatment

All subjects were required to use an additive-free, basic bland emollient twice daily (or more, as needed) for at least 14 days before randomisation. Subjects were not allowed to start treatment with prescription emollients or emollients containing additives such as ceramide, hyaluronic acid, urea, or filaggrin, unless initiated prior to the screening visit. Subjects were required to continue their background emollient treatment throughout the trial.

Concomitant medication

The following concomitant medications related to AD treatment were permitted from screening through safety follow-up (Week 66; Week 82 for selected Japanese subjects):

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

In addition, the use of topical treatments was permitted during safety follow-up (from Week 52 or Week 68 for selected Japanese subjects in ECZTRA 1) at the investigator's discretion.

Rescue treatment

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 during any of the treatment periods. For analysis of the primary estimand for the primary endpoints, subjects who received rescue treatment during the initial treatment period were considered as non-responders, but they continued IMP treatment if the rescue treatment consisted of topical medications only.

Use of rescue medication was recorded as concomitant medication.

Open-label tralokinumab arm only

From Week 16 through safety follow-up (Week 66; Week 82 for selected Japanese subjects in ECZTRA 1) 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

Primary objective

- To evaluate the efficacy of tralokinumab compared with placebo in treating moderate-to-severe AD.

Secondary objectives

- To evaluate the efficacy of tralokinumab on severity and extent of AD, itch, and Health-related quality of life (HRQoL) compared with placebo.

Outcomes/endpoints

Primary endpoints

- Investigator Global Assessment (IGA) score of 0 (clear) or 1 (almost clear) at Week 16;
- 75% reduction from baseline in the Eczema Area and Severity Index (EASI75) at Week 16.

Secondary endpoints for the initial treatment period (Week 0 to Week 16)- under multiplicity adjustment

- Change in SCORAD (SCORing Atopic Dermatitis) from baseline to Week 16;
- Reduction of Worst Daily Pruritus NRS (weekly average) ≥4 from baseline to Week 16;
- Change in Dermatology Life Quality Index (DLQI) score from baseline to Week 16.

Secondary endpoints for the maintenance treatment period – (Weeks 16 to 52 for responders at Week 16) - under multiplicity adjustment

- IGA of 0/1 at Week 52 among subjects with IGA of 0/1 at Week 16 achieved without rescue medication after initial randomisation to tralokinumab;
- EASI75 at Week 52 among subjects with EASI75 at Week 16 achieved without rescue medication after initial randomisation to tralokinumab.

Other additional secondary endpoints can be found in Table 34 and Table 35.

Sample size

Assuming a screening failure rate of 25%, approximately 1040 subjects were expected to be screened and approximately 780 subjects were planned to be randomised 3:1 to initial treatment (585 subjects to tralokinumab and 195 subjects to placebo). The sample size was chosen to ensure that sufficient safety information was collected and that a sufficient number of responders were re-randomised to maintenance treatment.

Primary endpoints

For the endpoint IGA 0/1 at Week 16, a sample size of 780 subjects randomised at 3:1 provided >99% nominal power to detect a difference between tralokinumab and placebo, assuming IGA 0/1 response rates of 30% and 10%, respectively, at a 5% 2-sided level of significance.

For the endpoint EASI75 at Week 16, a sample size of 780 would likewise provide >99% nominal power to detect a difference between tralokinumab and placebo at Week 16, assuming EASI75 response rates of 40% and 15%, respectively.

Maintenance endpoints

With an IGA response rate of 30% at Week 16, 175 IGA responders initially treated with tralokinumab were expected to be re-randomised in a 2:2:1 ratio into the maintenance treatment period (70 subjects on tralokinumab Q2W, 70 subjects on tralokinumab Q4W, and 35 subjects on placebo). Assuming IGA response rates at Week 52 of 80%, 50% and 5%, respectively for tralokinumab Q2W, tralokinumab Q4W, and placebo, the nominal power to show a difference at the 4% significance level would be >99% between tralokinumab Q2W and placebo and >99% between tralokinumab Q4W and placebo.

With an EASI75 response rate of 40% at Week 16, 235 EASI75 responders initially treated with tralokinumab were expected to enter the maintenance treatment period (94 subjects on tralokinumab Q2W, 94 subjects on tralokinumab Q4W, 47 subjects on placebo). Assuming EASI75 response rates at Week 52 of 90%, 55% and 5%, respectively for tralokinumab Q2W, tralokinumab Q4W, and placebo, the nominal power to show a difference at the 4% significance level would be >99% between tralokinumab Q2W and placebo and >99% between tralokinumab Q4W and placebo.

Randomisation

Eligible subjects were randomised to treatment with either tralokinumab or placebo in a 3:1 ratio (tralokinumab 300 mg Q2W: placebo Q2W) 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 in a 2:2:1 ratio (tralokinumab 300 mg Q2W: tralokinumab 300 mg Q4W: placebo Q2W) in the maintenance treatment period. Subjects were assigned to the lowest available randomisation number. The subject number was a 5-digit number. A central Interactive Web Response System (IWRS)/interactive voice response system was used to control the randomisation and stratification factors (region and disease severity), along with IMP supply chain and expiry tracking.

Blinding (masking)

Since tralokinumab and placebo were visually distinct and not matched for viscosity, the IMP was handled and administered by a qualified, unblinded Health Care Professional (HCP) at the site who was not involved in the management of trial subjects and who did not perform any of the assessments.

Statistical methods

All subjects randomised and exposed to initial treatment were included in the full analysis set (FAS) and were analysed for efficacy up to Week 16.

A maintenance analysis set was defined as all subjects who were re-randomised and exposed to maintenance treatment.

A safety analysis set was defined by excluding subjects from the FAS who either received no treatment with IMP and/or for whom no post-baseline safety data were available.

The statistical methodology in trials ECZTRA 1 and 2 used an estimand framework, that incorporated 2 main types of intercurrent events (initiation of rescue medication and permanent discontinuation of IMP).

The primary estimand for the primary endpoints was the treatment difference in response rates of IGA 0/1 and EASI75 after 16 weeks achieved without rescue medication, resulting from initiation of a treatment regimen with tralokinumab compared to a treatment regimen with placebo and regardless of treatment discontinuation. Data retrieved at Week 16 for subjects who had permanently discontinued IMP prior to Week 16 was included in the analysis. Subjects who prior to the Week 16 visit had received rescue medication were considered non-responders, reflecting an assumption that initiation of rescue medication indicates failure of the randomised treatment to achieve response, and that a (possible) observed positive response after initiation of rescue medication is not attributable to the randomised treatment. Missing data for subjects who did not attend the Week 16 visit and where rescue medication had not been used prior to Week 16, were imputed as non-responders.

The difference in response rates between treatment groups was analysed using the Cochran-Mantel-Haenszel test stratified by region (North America, Japan, and Europe) and baseline disease severity (IGA 3 or 4).

Three sensitivity analyses were specified for the primary estimand: 1) All subjects who have permanently discontinued IMP prior to Week 16 were to be imputed as non-responders, even if no rescue medication has been used; 2) If subjects have withdrawn due to an AE or due to lack of efficacy, they were to be considered non-responders, data missing for other reasons were to be imputed using last observation carried forward; 3) a tipping point analysis using multiple imputation in which subjects in the tralokinumab group with missing week 16 data were considered non-responders while missing week 16 data for subjects in the placebo arm who did not use rescue medication were imputed from a Bernoulli distribution with parameter p (ranging from 0 to 1).

Supplemental `hypothetical' and tertiary `treatment policy' estimands were also defined for the primary endpoints.

The primary estimand for the continuous secondary endpoints was the treatment difference in change from baseline to Week 16 in SCORAD and DLQI, respectively, if all subjects adhered to the treatment regimen in the sense that they did not discontinue IMP permanently and no rescue medication was made available before Week 16. Data collected after permanent discontinuation of IMP or after initiation of rescue medication was not to be included in the analysis. To ensure that all subjects were included in the analysis, the baseline value for these subjects was carried forward as the first post-baseline assessment, corresponding to imputing a change of 0 at the first post-baseline assessment.

The continuous secondary endpoints were analysed using a repeated measurements model on the post baseline responses up to Week 16 with an unstructured covariance matrix, Kenward-Roger approximation to estimate denominator degrees of freedom, and the mean modelled as follows (shown for change from baseline in SCORAD):

Change from baseline in SCORAD = treatment × visit + baseline SCORAD × visit + region + baseline IGA.

This model assumes that data is missing at random within each treatment arm. In a sensitivity analysis, it was assumed that missing data from subjects who discontinue treatment/receive rescue medication in the tralokinumab arm would resemble data from subjects from the placebo arm who did not discontinue treatment/receive rescue medication. Multiple imputation of missing data at Week 16

was to be performed using a pattern mixture model where missing data in the tralokinumab arm as well as the placebo arm was to be imputed from the placebo arm (copy-reference approach).

Supplemental `treatment policy' and `composite' estimands were also defined for the continuous secondary endpoints.

For maintenance of IGA 0/1 and EASI75, the difference in response rates between treatment groups at week 52 was analysed using the Cochran-Mantel-Haenszel test stratified by region. The definition of the primary estimand for these endpoints was similar to that for the primary endpoints measured at week 16.

For ECZTRA 1 and 2, to control the overall type 1 error rate, the primary analyses of the primary estimands for the primary and secondary endpoints for the initial and maintenance treatment was to follow a testing procedure combining sequential testing for the primary endpoints, the Holm method for the families of secondary and maintenance endpoints, and sequential testing within these families.

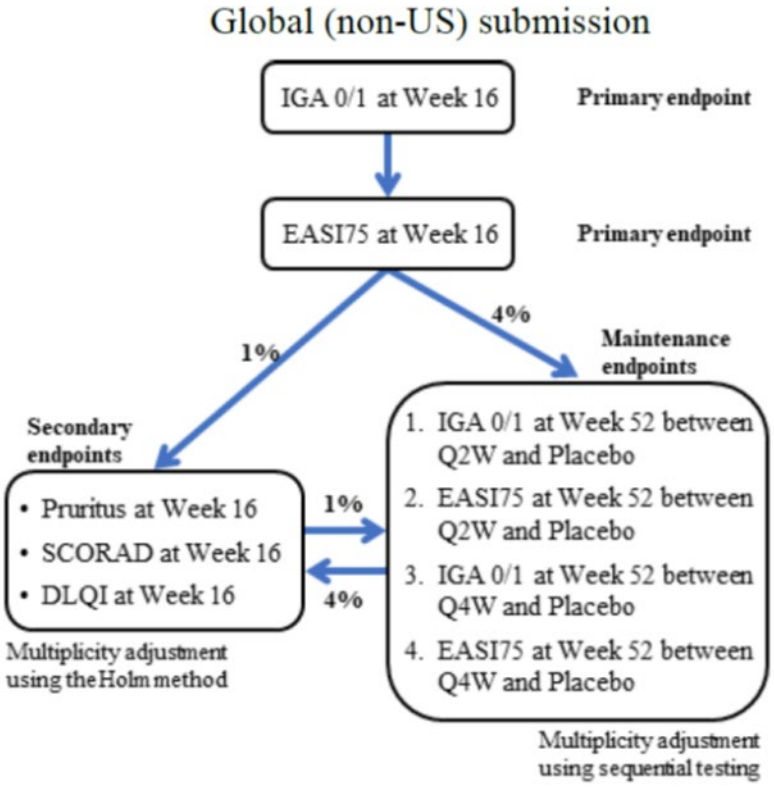
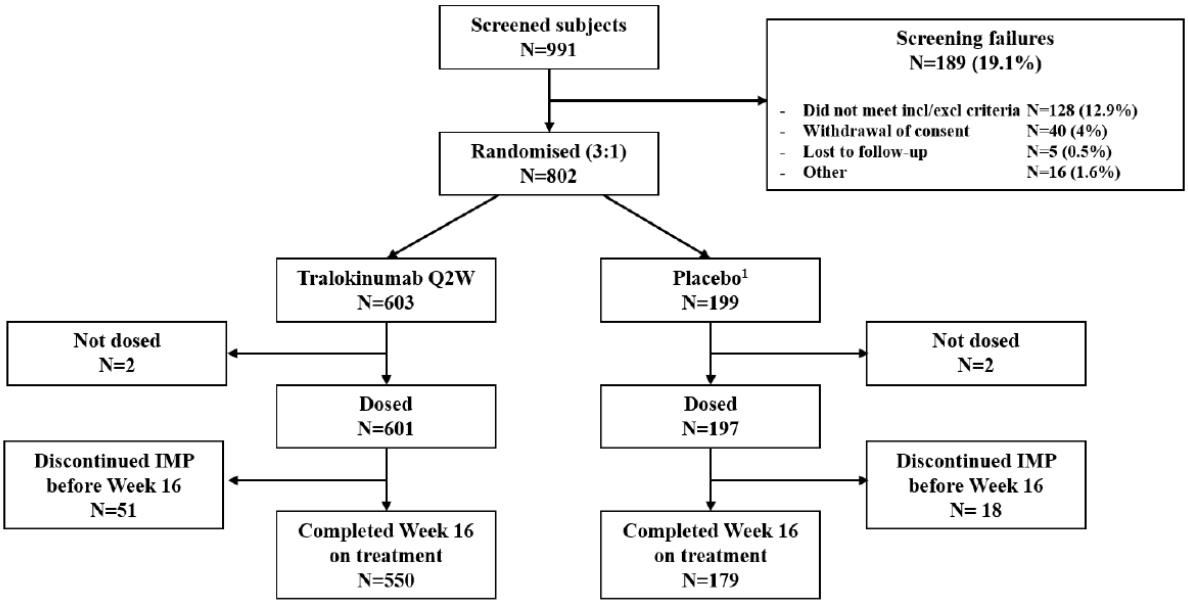


Figure 8 Type I error control – ECZTRA 1 and 2

Results

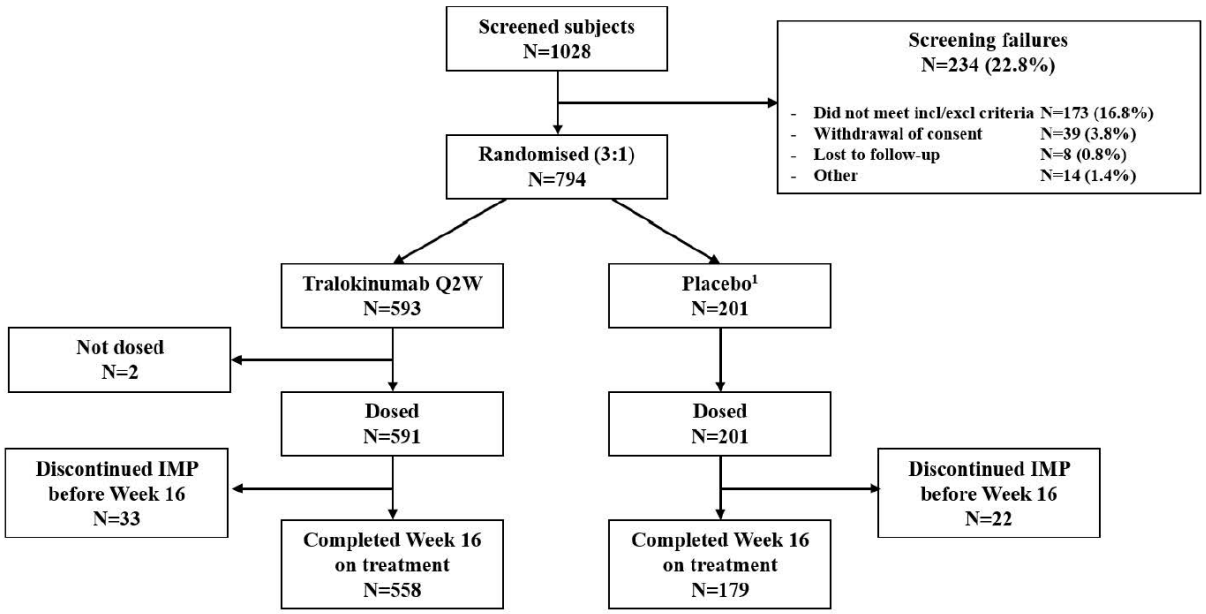
Participant flow

For both trials ECZTRA 1 and 2, a total of 1596 subjects were randomised; 1196 subjects to tralokinumab and 400 subjects to placebo. A total of 4 subjects in the tralokinumab and 2 subjects in the placebo group were not dosed, resulting in a FAS of 1192 subjects for tralokinumab and 398 subjects for placebo. The subject dispositions for the initial, maintenance and open-label treatment periods for ECZTRA 1 and 2 are presented on Figure 9 to Figure 14.



1) One subject was randomised to placebo and received one dose of tralokinumab at Week 0. In accordance with the statistical analysis plan, the subject was included as planned in the placebo arm when analysing efficacy and in the tralokinumab Q2W arm when analysing safety.

Figure 9 Subject disposition, initial treatment period – ECZTRA 1



1) One subject was randomised to placebo and received one dose of tralokinumab at Week 10. In accordance with the statistical analysis plan, the subject was included as planned in the placebo arm when analysing efficacy and in the tralokinumab Q2W arm when analysing safety.

Figure 10 Subject disposition, initial treatment period – ECZTRA 2

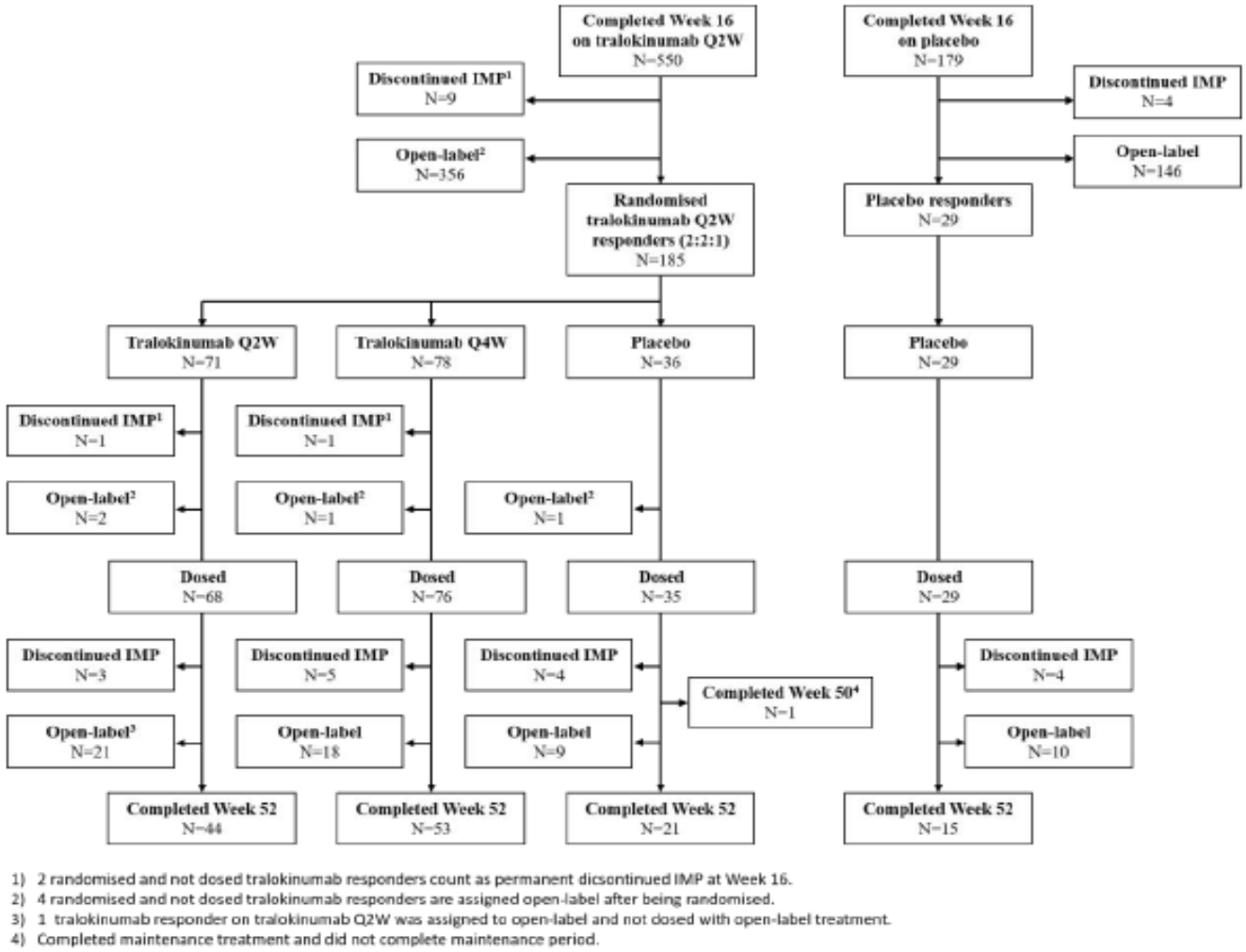
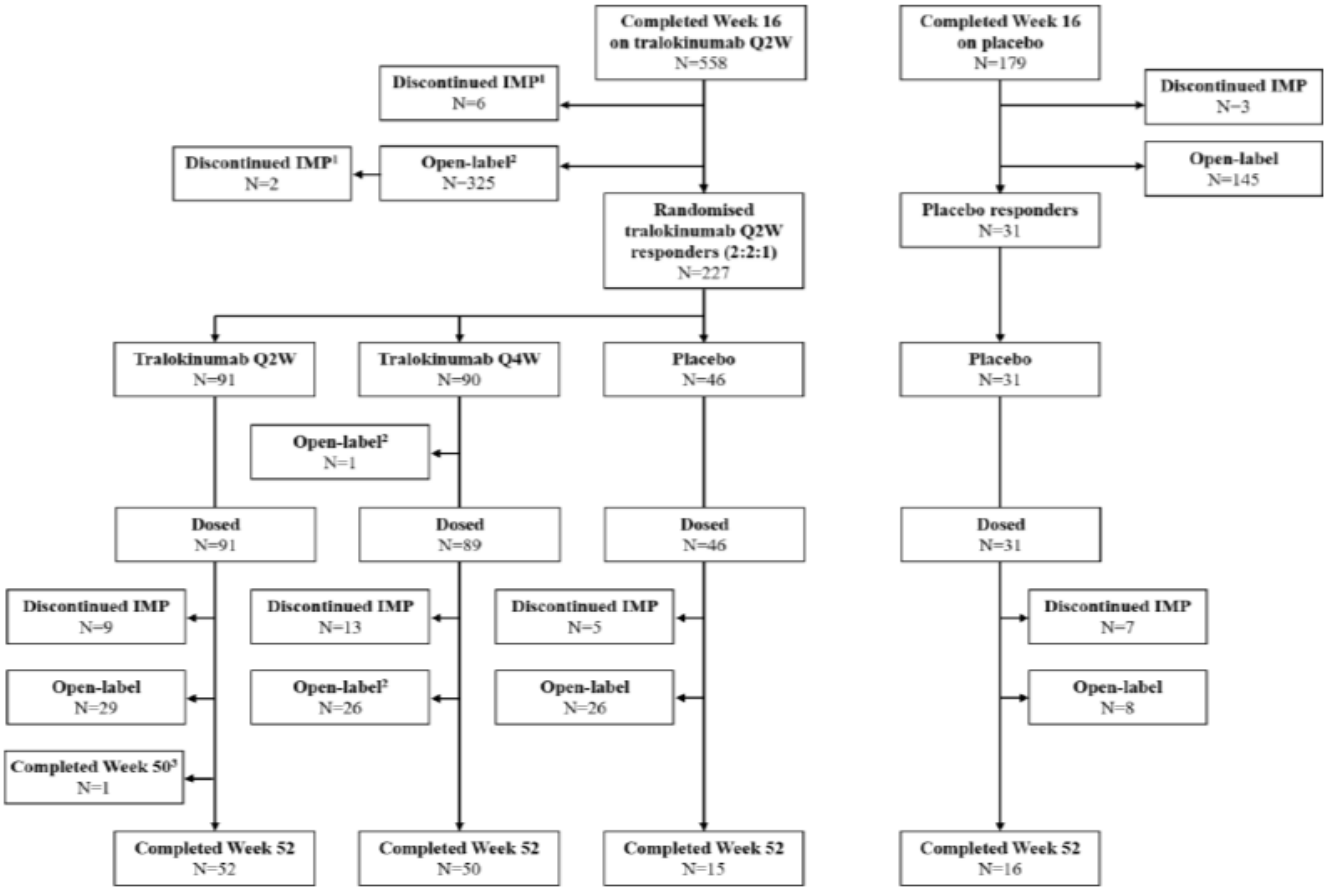


Figure 11 Subject disposition, maintenance treatment period- ECZTRA 1



1) 2 subjects assigned open-label treatment count as permanently discontinued IMP at Week 16.
2) 1 subject not responding to initial treatment with tralokinumab Q2W was randomised in error to maintenance treatment with tralokinumab Q4W and subsequently assigned open-label at Week 16 after being randomised. This subject contributes both to the number of subjects transferred to open-label treatment at Week 16 and the number of subjects transferred to open-label after being randomised to maintenance treatment.
3) 1 subject completed maintenance treatment and did not complete maintenance period.

Figure 12 Subject disposition, maintenance treatment period- ECZTRA 2

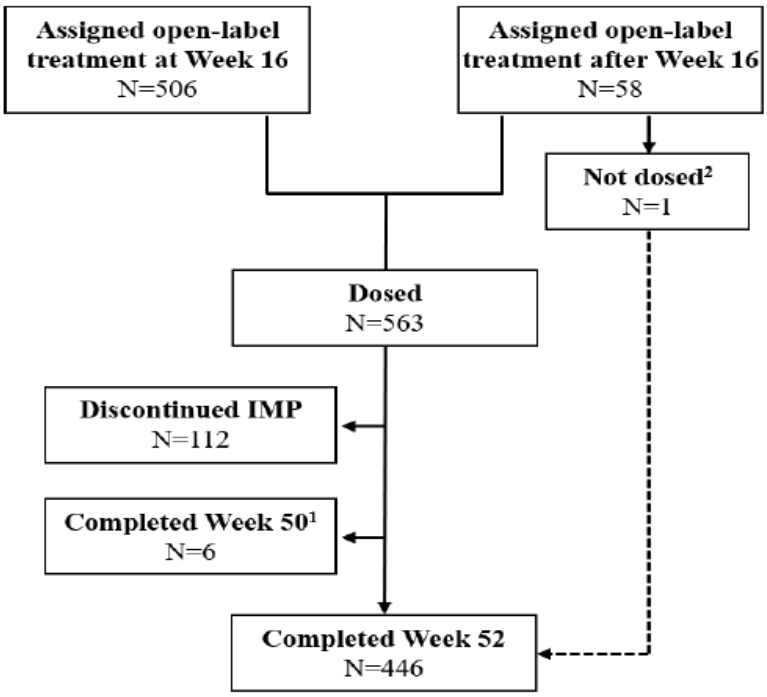


Figure 13 Subject disposition, open-label treatment- ECZTRA 1

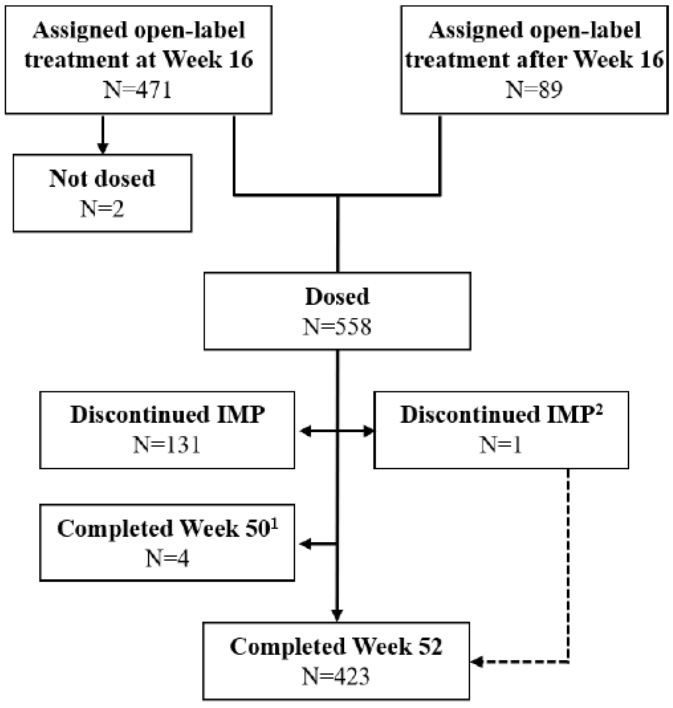


Figure 14 Subject disposition, open-label treatment- ECZTRA 2

Recruitment

ECZTRA 1

Date of first subject first visit: 30-May-2017.

Date of last subject last visit: 18-Jul-2019.

ECZTRA 2

Date of first subject first visit: 29-Jun-2017.

Date of last subject last visit: 14-Aug-2019.

Conduct of the study

ECZTRA 1

There were 3 global substantial amendments to the original protocol, dated 03 March 2017.

The first amendment (28 August 2017), assured the safety follow-up for all enrolled subjects, refined exclusion criteria, added one blood sample at week 4 and restricted eligible subjects for open-label period from IGA>1 to subjects who had both IGA>1 and not reached EASI75 reached. Amendment 2 (12 December2017), aimed mainly to refine different efficacy endpoints and maintenance period. Last amendment (14 August 2018), was regarding clarifications for eligibility for open label period, home use trainings, TCS treatment and collection of AEs in the ongoing long term study (ECZTEND).

Protocol deviations (PDs) were categorised as major or minor and into different categories according to a set of predefined categories. Major deviations were considered those related to violation of GCP, those that could significantly affect subject safety and wellbeing, and those that could potentially influence key efficacy parameters and thereby the outcome of the trial. A total of 431 major PDs were reported in this trial. No major PDs were reported at trial level. 4 major PDs at country-level, 20 major PDs at site-level and 407 major PDs at subject-level were reported during the trial (*Table 16*).

In total, 240 major PDs were related to study procedures. 231 PDs were reported at subject level and 9 PDs were reported at site level. 112/231 subject PDs constituted to various deviations in study procedures such as missed visits, visits performed out of window, missed assessments/procedures, or procedures not performed in accordance to the protocol.

11 subjects violated inclusion criteria relating Worst Daily Pruritus NRS average score of <4 during the week prior to baseline. These subjects were excluded from the NRS analysis.

The applicant stated that all protocol deviations were evaluated and considered not to impact subject safety or overall assessment of study results.

Table 16 Major subject-level protocol deviations by country: screened subjects

	Inclusion/Exclusion/ Randomisation Criteria		Informed Consent		SAE Reporting		Study Procedures		Trial Medication		Other		Total	
	n	PD	n	PD	n	PD	n	PD	n	PD	n	PD	n	PD
All (N=991)	29	36	61	77	5	5	160	232	36	39	16	18	257	407
United States (N=286)	14	21	22	28	2	2	41	64	14	15	6	6	76	136
Germany (N=309)	3	3	11	14	-		25	27	4	4	4	6	42	54
France (N=137)	1	1	8	9	2	2	27	42	10	11	4	4	45	69
Spain (N=111)	7	7	12	18	1	1	29	44	-		-		43	70
Japan (N=148)	4	4	8	8	-		38	55	8	9	2	2	51	78

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n: number of subjects with protocol deviations, N: total number of screened subjects (in a country), PD: number of protocol deviations.

ECZTRA 2

There were 4 global amendments to the original protocol, dated 17-Mar-2017. The first amendment (15-Jun-2017) was regarding clarifications of unblinding procedures. Last three amendments were similar to the amendments for ECZTRA 1 (at 28-Aug-2017, 12-Dec-2017 and 14-Aug-2018), as described above.

481 major PDs were reported in this trial. There were no major PDs reported at trial level. 3 major PDs at country level, 22 major PDs at site-level, and 456 major PDs at subject-level were reported (Table 17). In total, there were 257 subject-level and 8 site-level PDs related to study procedures. 169 subject PDs and 2 site-level PDs related to various other deviations in study procedures such as missed visits, visits performed out of window, missed assessments/procedures, or procedures not performed in accordance to the protocol.

18 subjects violated inclusion criteria relating to Worst Daily Pruritus NRS average score of <4 during the week prior to baseline. These subjects were excluded from the NRS analysis.

The applicant stated that all protocol deviations were evaluated and considered not to impact subject safety or overall assessment of study results.

Table 17 Major subject-level protocol deviations by country: screened subjects - POST-HOC

	Inclusion/Exclusion/ Randomisation Criteria		Informed Consent		SAE Reporting		Study Procedures		Trial Medication		Other		Total	
	n	PD	n	PD	n	PD	n	PD	n	PD	n	PD	n	PD
All (N=1028)	35	39	54	78	1	1	177	257	33	38	39	43	273	456
United States (N=236)	13	14	20	40	1	1	38	49	7	7	8	11	70	122
Australia (N=150)	3	4		-		-	19	20	2	3	3	3	27	30
Canada (N=251)	6	6	6	7		-	34	38	5	5	4	4	49	60
Denmark (N= 15)		-		-		-	1	1		-		-	1	1
Great Britain (N= 96)	5	6	10	10		-	16	20	8	8	17	18	41	62
Italy (N= 44)	5	6	12	12		-	27	68	8	12		-	34	98
Korea (N= 99)	2	2	6	9		-	18	27	2	2	2	2	23	42
Poland (N=116)	1	1		-		-	24	34	1	1	5	5	28	41
Russia (N= 21)		-		-		-		-		-		-		-

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Baseline data

Demographic and other baseline characteristics

Demographic and other baseline characteristics of patients recruited to the pivotal studies were similar. The overall mean age at baseline was 38.8 years in ECZTRA 1 and 36.7 years in ECZTRA 2. Only a small percentage of patients (<7%) enrolled to studies were elderly (i.e. >65 year of age). Overall, more than 55% of patients enrolled to the studies were men.

Subjects were included from 3 regions (North America (US) (24.7%), Europe (59.5%) and Asia (Japan) (15.8%)) in ECZTRA 1 and from 4 regions (North America (23.9% from Canada and 21.5% from US), Europe (29.5%), Australia (15.2%) and Asia(Korea) (9.8%) in ECZTRA 2.

The majority of subjects were White (70.3% in ECZTRA 1; 62.6% in ECZTRA 2), followed by Asian (20.0% in ECZTRA 1; 25.9% in ECZTRA 2) and Black or African American (7.4% in ECZTRA 1; 7.6% in ECZTRA 2). The mean weight and the mean Body Mass Index (BMI) of all randomised subjects were similar in ECZTRA 1 and ECZTRA 2 (i.e. 76.0 kg (range 37.0–165.0 kg) and BMI 26.0 kg/m2 (range 15.5–61.3 kg/m2 in ECZTRA 1 and 76.1 kg (range 42.0–156.0 kg) and mean BMI 26.3 kg/m2 (range 16.5–57.5 kg/m2) in ECZTRA 2).

Baseline disease severity

Disease severity and assessment at baseline were comparable between studies and between treatment groups.

The mean Body Surface Area (BSA) at the baseline was 53.1% in ECZTRA 1 and 52.7% in ECZTRA 2. Almost equal number of patients enrolled had moderate or severe disease (IGA 3 or 4). The mean EASI score was 32.4 in ECZTRA 1 and 32.2 in ECZTRA 2; the mean baseline Worst Daily Pruritus NRS was 7.7 in ECZTRA 1 and 7.9 in ECZTRA 2. The average age of AD onset was 10.5 years of age in ECZTRA 1 and 8.6 years of age in ECZTRA 2; the mean duration of AD at entry into the trials was around 28 years in both trials (Table 18). Mean baseline DLQI was 16.9 in ECZTRA 1 and 17.7 in ECZTRA 2; the baseline mean SCORAD score was 70.6 in ECZTRA 1 and 70.1 in ECZTRA 2, the baseline mean Patient Oriented Eczema Measure (POEM) score was 22.8 in both trials, the baseline

mean physical component of SF-36 were 44.5 in ECZTRA 1 and 44.3 in ECZTRA 2, and the baseline mean mental component was 43.6 in both trials.

Table 18 Disease severity at baseline in the pivotal trials ECTRA 1 and 2: all randomised

	ECZTRA 1		ECZTRA 2		ECZTRA 1+2	
	Tralokinumab Q2W (N=603)	Placebo (N=199)	Tralokinumab Q2W (N=593)	Placebo (N=201)	Tralokinumab Q2W (N=1196)	Placebo (N=400)
Baseline BSA (%)						
n	603	198	593	201	1196	399
Mean(SD)	52.7 (24.1)	54.2 (25.6)	52.6 (25.6)	53.0 (25.0)	52.7 (24.8)	53.6 (25.3)
Median	50.0	52.5	50.0	50.0	50.0	51.0
Min;Max	10;100	10;100	10;100	11;100	10;100	10;100
Age of AD onset (years)						
n	603	198	592	201	1195	399
Mean(SD)	10.7 (15.9)	9.7 (15.4)	8.9 (13.8)	7.7 (11.8)	9.8 (14.9)	8.7 (13.7)
Median	3.0	3.0	2.0	2.0	3.0	3.0
Min;Max	0;83	0;73	0;85	0;59	0;85	0;73
AD duration (years)						
n	603	198	592	201	1195	399
Mean(SD)	27.9 (14.5)	29.6 (15.1)	28.3 (15.9)	27.5 (14.7)	28.1 (15.2)	28.5 (14.9)
Median	27.0	28.0	25.5	25.0	26.0	26.0
Min;Max	1;71	1;77	1;74	1;73	1;74	1;77
IGA						
n	603	199	593	201	1196	400
Mod. disease	296 (49.1%)	95 (47.7%)	305 (51.4%)	100 (49.8%)	601 (50.3%)	195 (48.8%)
Sev. disease	305 (50.6%)	102 (51.3%)	286 (48.2%)	101 (50.2%)	591 (49.4%)	203 (50.8%)
Missing	2 (0.3%)	2 (1.0%)	2 (0.3%)		4 (0.3%)	2 (0.5%)
EASI score						
n	601	197	591	201	1192	398
Mean(SD)	32.2 (13.7)	32.9 (13.9)	32.1 (14.3)	32.6 (13.9)	32.2 (14.0)	32.7 (13.9)
Median	28.2	30.3	28.2	29.6	28.2	29.8
Min;Max	16.0;72.0	16.0;70.8	15.4;72.0	16.0;72.0	15.4;72.0	16.0;72.0
Worst Daily Pruritus NRS (weekly average)						
n	598	195	584	200	1182	395
Mean(SD)	7.7 (1.4)	7.7 (1.4)	7.9 (1.5)	8.0 (1.4)	7.8 (1.5)	7.8 (1.4)
Median	7.9	7.9	8.0	8.1	7.9	8.0
Min;Max	2.5;10.0	3.0;10.0	2.3;10.0	4.0;10.0	2.3;10.0	3.0;10.0

In term of symptoms and quality of life, the populations in both trials had a high burden of disease at baseline. The proportion of subjects with asthma at baseline ranged between 38-47% while 34-40% had food allergy and 44-56% had hay fever.

The most common prior AD treatments in the trials were topicals. TCS were used by 98.0% in ECZTRA 1 and 98.7% in ECZTRA 2 of subjects, and TCI by 50.0% in ECZTRA 1 and 46.5% in ECZTRA 2. Across trials and treatment groups, prior systemic AD medication included systemic steroids (59.4% in ECZTRA 1 and 67.4% in ECZTRA 2%), cyclosporine (36.4% in ECZTRA 1 and 33.9% in ECZTRA 2%), methotrexate (12.8% in ECZTRA 1 and 20.8% in ECZTRA 2%), azathioprine (5.7% in ECZTRA 1 and 12.2% in ECZTRA 2), mycophenolate (4.5% in ECZTRA 1 and 6.4% in ECZTRA 2) and other immunosuppressants (5.0% in ECZTRA 1 and 5.2% in ECZTRA).

The vast majority of rescue medication used was topical corticosteroids. The use of rescue medication was higher in subjects with severe disease at baseline than in subjects with moderate disease at baseline.

Numbers analysed

For the monotherapy trials, a total of 1596 subjects were randomised; 1196 subjects to tralokinumab and 400 subjects to placebo. A total of 4 subjects in the tralokinumab and 2 subjects in the placebo group were not dosed, resulting in a FAS of 1192 subjects for tralokinumab and 398 subjects for

placebo. The monotherapy trials were characterised by a high degree of subject retention in the initial treatment period. Of the 1596 randomised subjects, 124 (7.8%) permanently discontinued treatment before Week 16 with a slightly lower discontinuation rate in the tralokinumab group (7.0%) compared to the placebo group (10.0%).

Outcomes and estimation

Initial treatment period

Primary endpoints

- *IGA 0/1 at Week 16*

In ECZTRA 1 and 2, 15.8% and 22.2% of subjects treated with tralokinumab achieved IGA 0/1 at Week 16 compared to 7.1% and 10.9% of subjects treated with placebo, respectively. The treatment difference between tralokinumab and placebo was slightly higher in ECZTRA 2 (11.1%) compared to ECZTRA 1 (8.6%).

Treatment differences and the corresponding 95% CIs from the analyses for the 3 estimands defined for IGA 0/1 at Week 16 are presented in Figure 15.

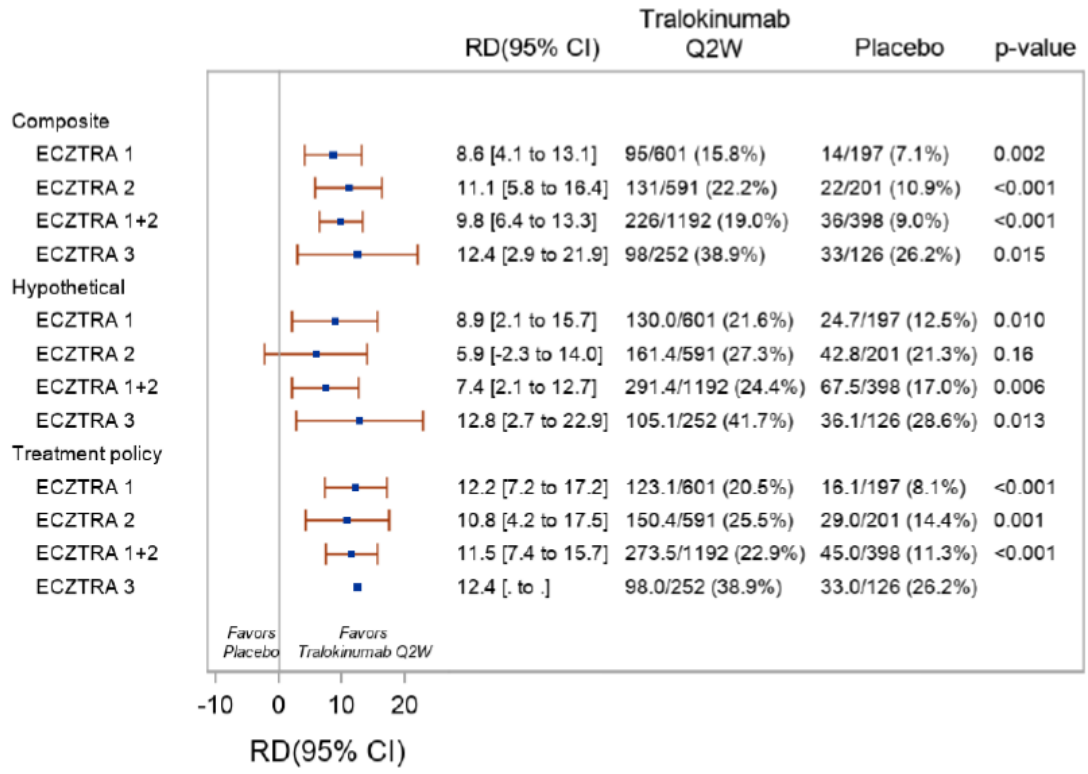
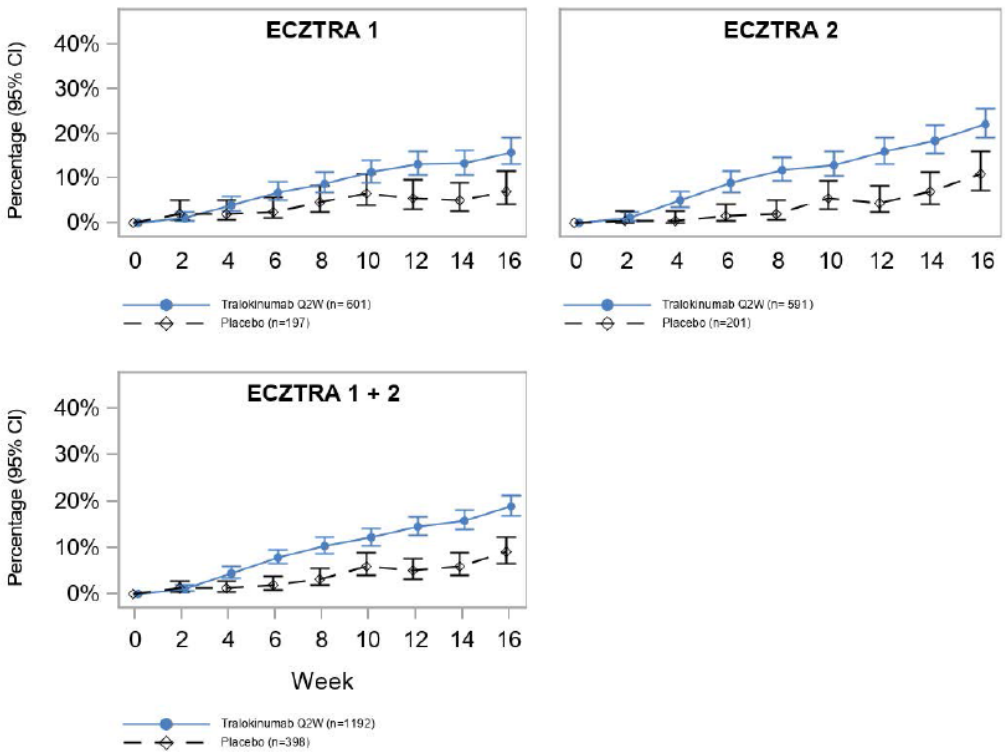


Figure 15 Forest plot of IGA 0/1 at Week 16 for the pivotal phase 3 trials and ECZTRA 1+2, initial treatment period: FAS

For this monotherapy pool, 19.0% of subjects were responders in the tralokinumab group compared to 9.0% in the placebo group leading to a treatment difference of 9.8% (p<0.001) based on the composite estimand (Figure 16).



Notes: Subjects who received rescue medication considered non-responders. Subjects with missing data imputed as non-responders.
Abbreviations: CI = confidence interval; FAS = full analysis set; IGA = Investigator's Global Assessment, TCS = topical corticosteroids.

Figure 16 IGA 0/1 by week for the pivotal phase ECTRZA 1 and 2 trials and ECZTRA 1+2, initial treatment period: FAS

- *EASI-75 at Week 16*

Treatment differences and the corresponding 95% CIs from the analyses for EASI75 at Week 16 are presented in Figure 17.

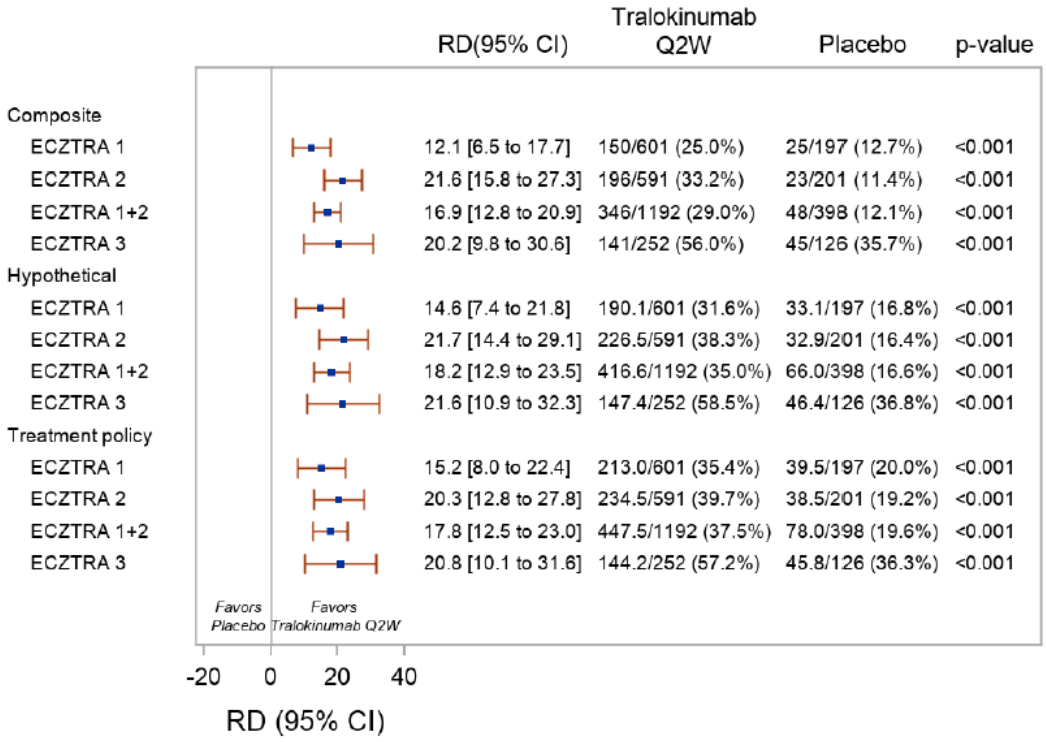
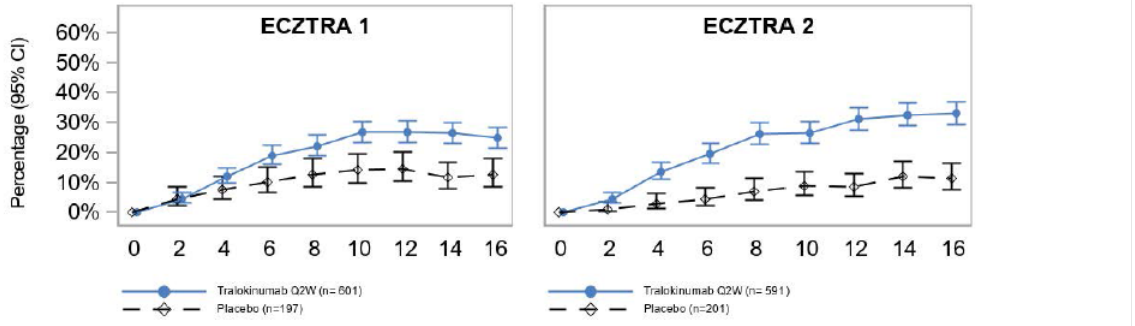
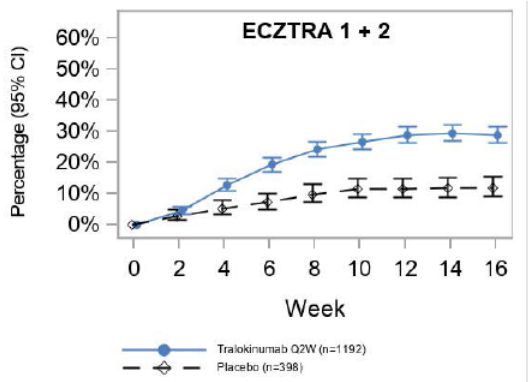


Figure 17 Forest plot of EASI75 at Week 16 for the pivotal phase 3 trials ECZTRA 1+2, initial treatment period: FAS

For both ECZTRA 1 and ECZTRA 2, the proportion of EASI75 responders at Week 16 was higher in the tralokinumab group (25.0% in ECZTRA 1 and 33.2% in ECZTRA 2) compared to the placebo group (12.7% in ECZTRA 1 and 11.4% in ECZTRA 2) based on the primary analysis of the composite estimand ($p<0.001$ for both ECZTRA 1 and ECZTRA 2). The treatment difference between tralokinumab and placebo was higher in ECZTRA 2 (21.6%) compared to ECZTRA 1 (12.1%). In general, an increase in the proportion of EASI75 responders was observed up until around Week 10-12 with a steeper increase in the tralokinumab group compared to placebo (Figure 18).





Notes: subjects who received rescue medication considered non-responders. Subjects with missing data imputed as non-responders.
Abbreviations: CI = confidence interval, EASI75 = at least 75% reduction in EASI score; EASI = Eczema Area and Severity Index; FAS = full analysis set; TCS = topical corticosteroids.

Figure 18 EASI75 by week for the pivotal phase 3 trials and ECZTRA 1+2, initial treatment period: FAS

Key secondary endpoints

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

For both ECZTRA 1 and ECZTRA 2, the proportion of responders at Week 16 was higher in the tralokinumab group (20.0% in ECZTRA 1 and 25.0% in ECZTRA 2) compared to the placebo group (10.3% in ECZTRA 1 and 9.5% in ECZTRA 2) based on the primary analysis of the composite estimand (p=0.002 for ECZTRA 1, p<0.001 for ECZTRA 2). This leads to treatment differences of mean (95%CI) of 9.7 (4.4-15.0) in ECZTRA 1 and 15.6 (10.3-20.9) in ECZTRA 2 (Figure 19).

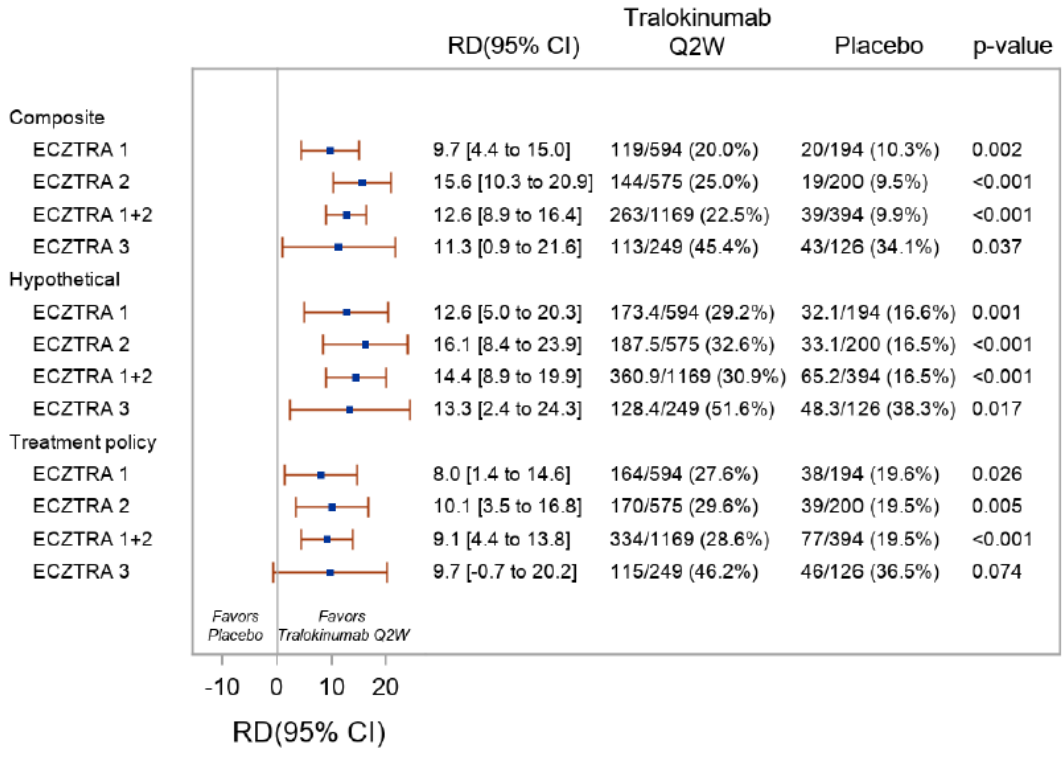


Figure 19 Forest plot of reduction of Worst Daily Pruritus NRS (weekly average) of at least 4 from baseline to Week 16 for the pivotal phase 3 trials and ECZTRA 1+2, initial treatment period: FAS

- *Change in SCORAD from baseline to Week 16*

For the monotherapy pool, there was an adjusted mean change from baseline to Week 16 in SCORAD of -26.5 in the tralokinumab group and -14.3 in the placebo group leading to a treatment difference of -12.3 (p<0.001) for the hypothetical estimand. When considering the treatment policy estimand, the treatment difference was -10.4 (p<0.001) with an adjusted mean change of -28.5 in the tralokinumab group and -18.1 in the placebo group (p<0.001) (Table 19).

Table 19 Change from baseline in SCORAD at Week 16 for the pivotal phase 3 trials and ECZTRA 1+2, initial treatment period: FAS

	ECZTRA 1		ECZTRA 2		ECZTRA 1+2	
	Tralo Q2W (N=601)	Placebo (N=197)	Tralo Q2W (N=591)	Placebo (N=201)	Tralo Q2W (N=1192)	Placebo (N=398)
Primary estimand: hypothetical[a]						
n	601	197	591	201	1192	398
Adj. mean change	-25.2	-14.7	-28.1	-14.0	-26.5	-14.3
(SE)	(0.94)	(1.80)	(0.92)	(1.79)	(0.66)	(1.27)
Diff.	-10.4		-14.0		-12.3	
(95% CI)	(-14.4,-6.5)		(-18.0,-10.1)		(-15.1,-9.5)	
p-value	<0.001		<0.001		<0.001	
Secondary estimand: treatment policy[b]						
n	601	197	591	201	1192	398
Adj. mean change	-28.3	-18.5	-28.8	-17.7	-28.5	-18.1
(SE)	(0.81)	(1.62)	(1.04)	(1.86)	(0.66)	(1.31)
Diff.	-9.8		-11.1		-10.4	
(95% CI)	(-13.3,-6.2)		(-15.3,-6.9)		(-13.3,-7.5)	
p-value	<0.001		<0.001		<0.001	
Tertiary estimand: composite[c]						
n	601	197	591	201	1192	398
Adj. mean change	-17.9	-7.3	-23.0	-7.4	-20.4	-7.3
(SE)	(0.86)	(1.50)	(0.91)	(1.58)	(0.63)	(1.09)
Diff.	-10.6		-15.7		-13.1	
(95% CI)	(-13.9,-7.2)		(-19.2,-12.1)		(-15.6,-10.6)	
p-value	<0.001		<0.001		<0.001	

a) Data collected after permanent discontinuation of IMP or initiation of rescue medication not included. In case of no post-baseline assessments before initiation of rescue medication, the Week 2 change/percentage change was imputed as 0. Repeated measurements analysis.

b) All data used as observed at Week 16. Multiple imputation of missing values. ANCOVA model at Week 16: Change in SCORAD = Treatment + Baseline SCORAD + region + Baseline IGA + trial ID (trial ID only for the integrated analysis).

c) Worst observation carried forward for all subjects who received rescue medication. Multiple imputation of missing values for subjects who did not receive rescue medication. ANCOVA model as above.

- *Change in DLQI score from baseline to Week 16*

For the monotherapy pool, there was an adjusted mean change from baseline to Week 16 in DLQI of -8.0 in the tralokinumab group and -5.0 in the placebo group leading to a treatment difference of -3.0 (p<0.001) based on the hypothetical estimand (Table 20).

Table 20 Change from baseline in DLQI at Week 16 for the pivotal phase 3 trials and ECZTRA 1+2, initial treatment period: FAS

	ECZTRA 1		ECZTRA 2		ECZTRA 1+2	
	Tralo Q2W (N=601)	**Placebo (N=197)**	**Tralo Q2W (N=591)**	**Placebo (N=201)**	**Tralo Q2W (N=1192)**	**Placebo (N=398)**
Primary estimand: hypothetical[a]						
n	601	197	591	201	1192	398
Adj. mean change (SE)	-7.1 (0.31)	-5.0 (0.59)	-8.8 (0.30)	-4.9 (0.60)	-8.0 (0.22)	-5.0 (0.42)
Diff. (95% CI)	-2.1 (-3.4,-0.8)		-3.9 (-5.2,-2.6)		-3.0 (-3.9,-2.0)	
p-value	0.002		<0.001		<0.001	
Secondary estimand: treatment policy[b]						
n Adj. mean change (SE) Diff. (95% CI) p-value	Not done[d]		Not done[d]		Not done[d]	
Tertiary estimand: composite[c]						
n	601	197	591	201	1192	398
Adj. mean change (SE)	-4.8 (0.30)	-2.0 (0.52)	-7.0 (0.32)	-1.9 (0.55)	-5.9 (0.22)	-2.0 (0.38)
Diff. (95% CI)	-2.7 (-3.9,-1.6)		-5.1 (-6.3,-3.9)		-3.9 (-4.8, -3.1)	
p-value	<0.001		<0.001		<0.001	

a) Data collected after permanent discontinuation of IMP or initiation of rescue medication not included. In case of no post-baseline assessments before initiation of rescue medication, the Week 2 change/percentage change will be imputed as 0. Repeated measurements analysis.

b) All data used as observed at Week 16. Multiple imputation of missing values. ANCOVA model at Week 16: Change in DLQI = Treatment + Baseline DLQI + region + Baseline IGA + trial ID (trial ID only for the integrated analysis).

c) Worst observation carried forward for all subjects who received rescue medication. Multiple imputation of missing values for subjects who did not receive rescue medication. ANCOVA model as above.

d) The secondary estimand ('treatment policy') could not be performed, since there was not enough retrieved data at Week 16 in the placebo group in ECZTRA 1 and 2 to perform the pre-specified imputation approach.

- *Other endpoints results*

Other relevant endpoints are presented in *Table 21*.

Table 21 Other endpoints results of Adtralza monotherapy at Week 16 in ECZTRA 1 and ECZTRA 2

Monotherapy				
	ECZTRA 1 week 16		**ECZTRA 2 week 16**	
	Placebo	**Adtralza 300 mg Q2W**	**Placebo**	**Adtralza 300 mg Q2W**
Patients randomised	199	603	201	593
Eczema-related sleep NRS, LS mean change from baseline (SE)[a)]	-1.9 (0.2)	-2.6[#] (0.1)	-1.5 (0.2)	-2.9[§] (0.1)
POEM, LS mean change from baseline (SE)[a)]	-3.0 (0.7)	-7.6[§] (0.4)	-3.7 (0.7)	-8.8[§] (0.3)
POEM (≥4-point improvement), % responders[b)]	18.0% (35/194)	43.0%[§] (253/588)	22.1% (44/199)	54.4%[§] (319/586)

LS: Least squares, SE: Standard error
If needed to control intolerable symptoms of atopic dermatitis, patients were permitted to receive rescue treatment at the discretion of the investigator.
a) Data after initiation of rescue medication or permanent discontinuation of treatment was excluded from the analyses.
b) Subjects who received rescue treatment or had missing data were treated as non-responders. The percentage is calculated relative to the number of subjects with POEM ≥4 at baseline.
*p<0.05, [#]p<0.01, [§]p<0.001

Maintenance period

In studies ECZTRA 1 and 2, in the maintenance treatment period, 2 secondary endpoints were under confirmatory strategy: IGA 0/1 at Week 52 among subjects who achieved IGA 0/1 at Week 16 without rescue medication and EASI75 at Week 52 among subjects who achieved EASI75 at Week 16 without rescue medication.

- IGA 0/1 at Week 52 among subjects with IGA 0/1 at Week 16

In ECZTRA 1, in the tralokinumab Q2W group, the proportion of subjects who maintained the IGA 0/1 response at Week 52 was 51.3%, while in the tralokinumab Q4W group, the proportion was lower with 38.9%. A relatively higher proportion of subjects maintained clinical response of IGA 0/1 in the placebo group (47.4%) compared with tralokinumab Q4W group (38.9%) (p>0.05 compared to placebo) (Table 22).

Similarly, in ECZTRA 2, in the tralokinumab Q2W group, the proportion of subjects who maintained the IGA 0/1 response at Week 52 was 59.3%, while in the tralokinumab Q4W group, the proportion was lower with 44.9%. A statistically significant treatment difference compared to placebo of 34.1% (95%CI: 13.4 to 54.9, p-value=0.004) was only observed in tralokinumab Q2W group based on the primary analysis. The sensitivity analysis did not change the conclusion of the primary analysis (Table 22).

- EASI75 at Week 52 among subjects with EASI75 at Week 16

In ECZTRA 1, in the tralokinumab Q2W group, the proportion of subjects who maintained EASI75 response at Week 52 was 59.6%. In the tralokinumab Q4W group, the proportion was slightly lower with 49.1% and lowest in the placebo group with 33.3% (Table 22).

In ECZTRA 2, in the tralokinumab Q2W group, the proportion of subjects who maintained EASI75 response at Week 52 was 55.8%. In the tralokinumab Q4W group, the proportion was slightly lower with 51.4% and lowest in the placebo group with 21.4%. The proportion of EASI75 responders at Week 52 was statistically significantly higher only in the tralokinumab Q2W group compared with placebo. The sensitivity analysis did not change the conclusion of the primary analysis (Table 22).

Given the testing hierarchy, and that IGA 0/1 at Week 52 for tralokinumab Q4W compared with placebo was not statistically significant EASI75 at Week 52 for tralokinumab Q4W compared to placebo was not evaluated with regards to statistical significance.

Table 22 Efficacy results (IGA 0 or 1 or EASI-75) at week 52 of subjects responding to Adtralza 300 mg Q2W at week 16

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

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

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

b) p<0.001 compared to placebo

c) p<0.05 compared to placebo

d) p>0.05 compared to placebo

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

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

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

Results for other secondary endpoints can be found in Table 34 and Table 35.

Open label period (ECZTRA 1 and 2)

The data from the open-label treatment period was not integrated for ECZTRA 1 and 2.

ECZTRA 1

Among the 506 subjects who transferred to open-label treatment at Week 16, 20.4% (95% CI: 17.1 to 24.1) of the subjects achieved IGA 0/1 at Week 28 and 24.3% (95% CI: 20.8 to 28.2) achieved IGA 0/1 at Week 52. 75 out of the 360 non-responders (20.8%) transferring from the tralokinumab group achieved IGA 0/1 at Week 52. 48 out of the 146 non-responders (32.9%) transferring from the placebo group achieved IGA 0/1 at Week 52 (Figure 20).

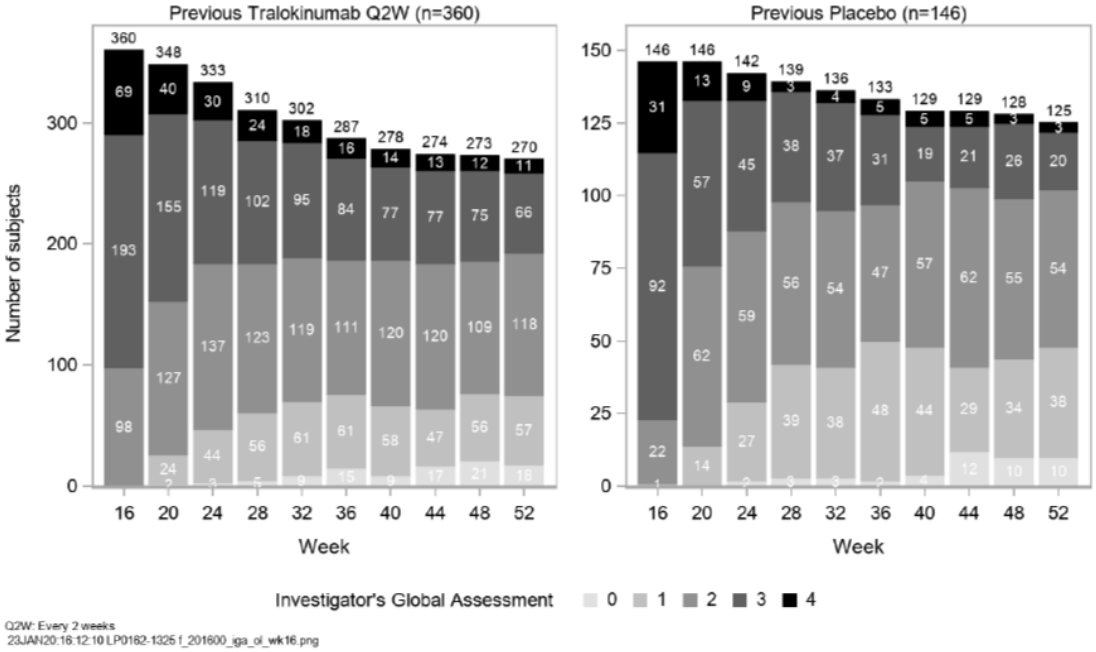


Figure 20 ECZTRA1: IGA by visit and by initial treatment, open-label treatment, observed cases: subjects transferred to open-label treatment at Week 16

ECZTRA 2

During the open label period in ECZTRA 2, 63 out of the 326 non-responders (19.3%) transferring from the tralokinumab group at Week 16 achieved IGA 0/1 at Week 52. 43 out of the 145 non-responders (29.7%) transferring from the placebo group at Week 16 achieved IGA 0/1 at Week 52 (Figure 21).

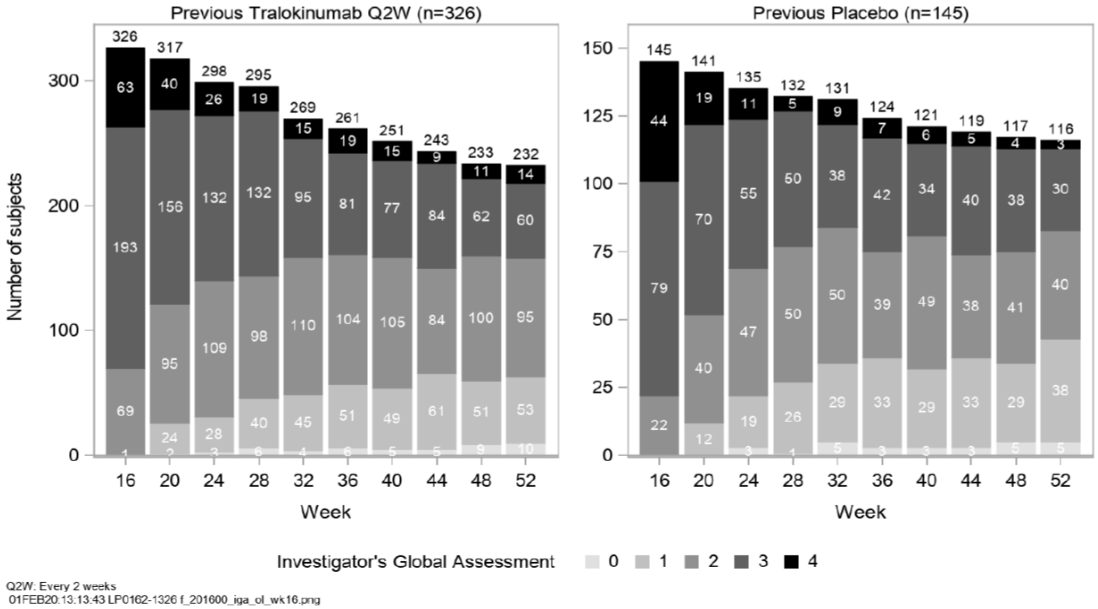


Figure 21 ECZTRA2: IGA by visit and by initial treatment, open-label treatment, observed cases: subjects transferred to open-label treatment at Week 16

ECZTRA 3

Methods

This was a randomised, double-blind, placebo-controlled, phase 3 trial to evaluate the efficacy and safety of tralokinumab in combination with topical corticosteroids in subjects with moderate-to severe AD 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, and a continuation treatment period of 16 weeks. After completion of the continuation treatment period, all subjects, except for those who entered the open-label long-term extension trial (ECZTEND), continued in a 14-week off-treatment follow-up period for the assessment of safety.

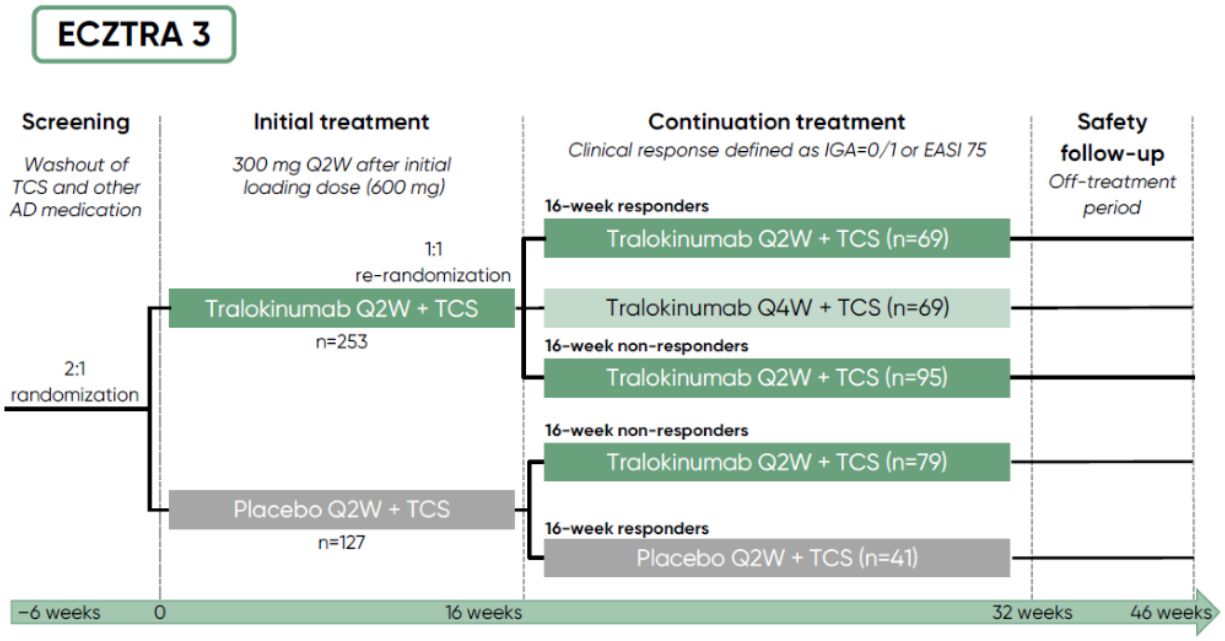


Figure 22 Trial design ECZTRA 3

Study Participants

The main inclusion and exclusion criteria for ECZTRA 3 were the same as for ECZTRA 1 and 2 (see 'Study Participants' for ECZTRA 1 and 2).
Patients who cannot tolerate treatment with topical corticosteroids were excluded from ECZTRA 3

Treatments

Initial treatment period

In the initial treatment period, each subject received their first dose of IMP on Day 0 (baseline) as 4 SC injections (1.0 mL each) of 150 mg tralokinumab or placebo to receive a total loading dose of 600 mg tralokinumab or placebo (4.0 mL).

At subsequent visits in the initial treatment period, each subject received 2 SC injections (1.0 mL each) of 150 mg tralokinumab Q2W or placebo Q2W to receive a total dose of 300 mg tralokinumab or placebo.

Continuation treatment period

In the continuation treatment period, each subject received either:

- Tralokinumab Q2W (2 SC injections [1.0 mL each] of 150 mg tralokinumab);
- Tralokinumab Q4W (alternating dose administrations: 2 SC injections [1.0 mL each] of 150 mg tralokinumab and 2 SC injections [1.0 mL each] of placebo);
- Placebo Q2W (2 SC injections [1.0 mL each] of placebo);

Subjects received the last dose of IMP at Week 30.

Background treatment

The subjects were instructed to apply a thin film of the dispensed TCS (mometasone furoate, 0.1% cream) once daily to active lesions from Week 0 to Week 32, as needed and were to discontinue treatment with TCS when control was achieved.

Discontinuation of TCS should preferably be gradual and the duration of treatment should not exceed 3 weeks. The safety and appropriateness of continued or repeated courses of TCS therapy was monitored and supervised by site staff.

An additional, lower potency TCS or TCI could be used at the investigator's discretion on areas of the body where use of the supplied TCS was not advisable such as areas of thin skin (face, skin fold areas, genital areas, etc.) or on areas where continued treatment was considered unsafe.

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 emollient should preferable be an additive-free, basic bland emollient. Subjects were required to continue their background emollient treatment throughout the trial (including during the safety follow-up period). On lesional skin, emollients should only be applied at times where TCS was not applied (i.e. emollients and TCS should not to be used on the same areas at the same time of day). On TCS-untreated areas, the emollients could be applied at all times.

In addition to stable doses of emollient, the following concomitant medications for treatment of AD were permitted from Week -6/-2 (screening) to Week 46 (end of safety follow-up):

- Oral antibiotics, antiviral, or antifungal therapy for skin infections, as appropriate;
- Oral anti-histamines.

Rescue treatment

If medically necessary (i.e. to control intolerable AD symptoms), rescue treatment for AD could be provided to subjects at the discretion of the investigator. Rescue medication include topical and systemic treatment.

Subjects who received topical rescue treatment (higher potency TCS: Europe Class >3; US Class >4) continued treatment with the IMP.

Subjects who received systemic rescue treatment with corticosteroids or non-steroidal immunosuppressive drugs (cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, etc.)

were required to immediately discontinue IMP. After treatment with these medications was completed, treatment with the IMP could be resumed if deemed necessary.

Objectives

Primary objective

- To evaluate the efficacy of tralokinumab compared with placebo in treating moderate-to-severe AD.

Secondary objectives

- To evaluate the efficacy of tralokinumab on severity and extent of AD, itch, and HRQoL compared with placebo.

Outcomes/endpoints

Primary endpoints

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

Secondary endpoints for the initial treatment phase – under multiplicity adjustment

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

Secondary endpoints for the maintenance phase

- IGA 0/1 at Week 32;
- EASI71 at Week 32.

Additional secondary endpoints can be found in Table 36.

Sample size

Assuming a screening failure rate of 25%, approximately 492 subjects were planned to be screened and approximately 369 subjects were planned to be randomised 2:1 to the initial treatment; 246 subjects to tralokinumab Q2W+TCS and 123 subjects to placebo+TCS.

For the single endpoint IGA 0/1 at Week 16, a sample size of 369 subjects randomised 2:1 would provide 90% power to detect a difference between the 2 arms, assuming response rates of 30% for tralokinumab+TCS and 15% for placebo+TCS.

For the single endpoint EASI75 at Week 16, a sample size of 369 would provide a nominal power >99.9% to detect a difference between tralokinumab+TCS and placebo+TCS, assuming EASI75 response rates of 40% and 15%, respectively.

The combined power for demonstrating a significant difference for both endpoints is therefore effectively also 90% with a sample size of 369 subjects, even when assuming no correlation between the 2 primary endpoints. In all cases, the evaluations were to be made with a 2-sided 5% significance level.

Randomisation

At Day 0 (baseline), eligible subjects were randomised to treatment with either tralokinumab or placebo in a 2:1 ratio stratified by region (Europe and North America) and baseline disease severity (IGA 3 or 4).

At Week 16, subjects were assigned a continuation treatment based on the initial treatment received and their clinical response at Week 16. Subjects initially randomised to tralokinumab who had a clinical response at Week 16 were re-randomised to treatment with either tralokinumab Q2W or tralokinumab Q4W in a 1:1 ratio stratified by region (Europe and North America) and IGA response at Week 16 (IGA 0/1 or IGA >1).

Subjects randomised to placebo in the initial treatment period who had a clinical response at Week 16 continued on placebo Q2W in the continuation treatment period via blinded treatment allocation.

Subjects randomised to either tralokinumab or placebo in the initial treatment period who had not achieved a clinical response at Week 16 were allocated to tralokinumab Q2W in the continuation treatment period.

Subjects were assigned to the lowest available randomisation number. The subject number was a 5-digit number. A central IWRS/interactive voice response system was used to control the randomisation and stratification factors.

Blinding (masking)

Tralokinumab and placebo were administered SC with matching injection volumes and frequencies to maintain blinding. However, tralokinumab and placebo were visually distinct from each other and not matched for viscosity. They were therefore handled and administered by a qualified unblinded HCP at each site who was not involved in the management of trial subjects and who did not perform any of the assessments.

Statistical methods

All subjects randomised to initial treatment were included in the FAS and were analysed for efficacy up to Week 16.

A continuation treatment analysis set was defined as subjects who have not withdrawn from trial prior to or at the Week 16 visit. Subjects who were not exposed to continuation treatment were excluded from the continuation treatment analysis set.

A safety analysis set was defined by excluding subjects from the full analysis set who either received no treatment with IMP and/or for whom no post-baseline safety data were available.

Similar statistical methodology was applied in ECZTRA 3 as in the ECZTRA 1 and ECZTRA 2 studies. Estimand definitions and analyses of the primary and secondary endpoints measured at week 16 were as described for the ECZTRA1 and ECZTRA2 studies. All efficacy analyses were based on the FAS, except for the secondary endpoint Worst NRS reduction ≥4, which was based on subjects in the FAS with a baseline Pruritus NRS weekly average ≥4.

For ECZTRA 3, to control the overall type 1 error rate, the primary analyses of the primary estimands for the primary and secondary endpoints for the initial treatment followed a testing procedure combining sequential testing for the primary endpoints, the Holm method for the family of secondary endpoints, and sequential testing within these families.

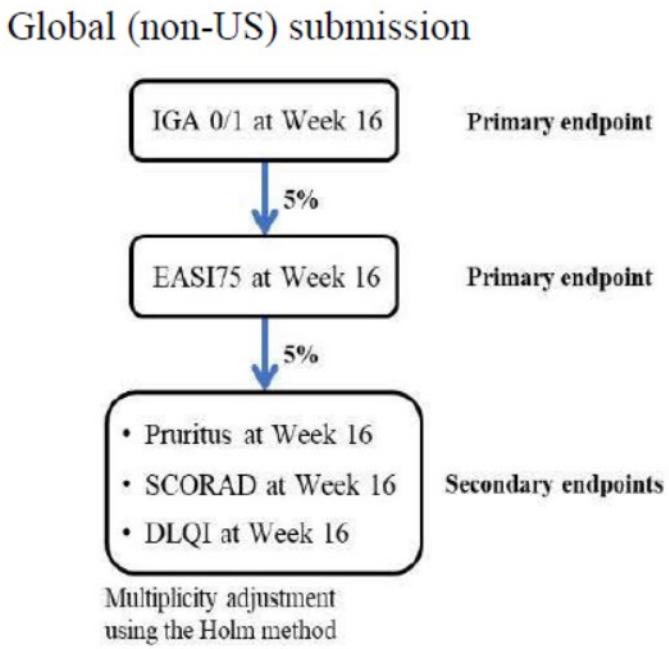


Figure 23 Type I error control – ECZTRA 3

Descriptive statistics were used for endpoints in the continuation treatment period. All efficacy analyses related to endpoints and assessments in the continuation treatment period were performed on the continuation analysis set and analysed according to their re-randomised/assigned treatment group.

Results

Participant flow

For this trial, 507 subjects were screened. 235 subjects (92.9%) in the tralokinumab Q2W+TCS group and 120 subjects (94.5%) in the placebo+TCS group completed the initial treatment period on treatment. Of these, 227 subjects (89.7%) in the tralokinumab Q2W+TCS group and 108 subjects (85.0%) in the placebo+TCS group completed the initial treatment period without using rescue medication.

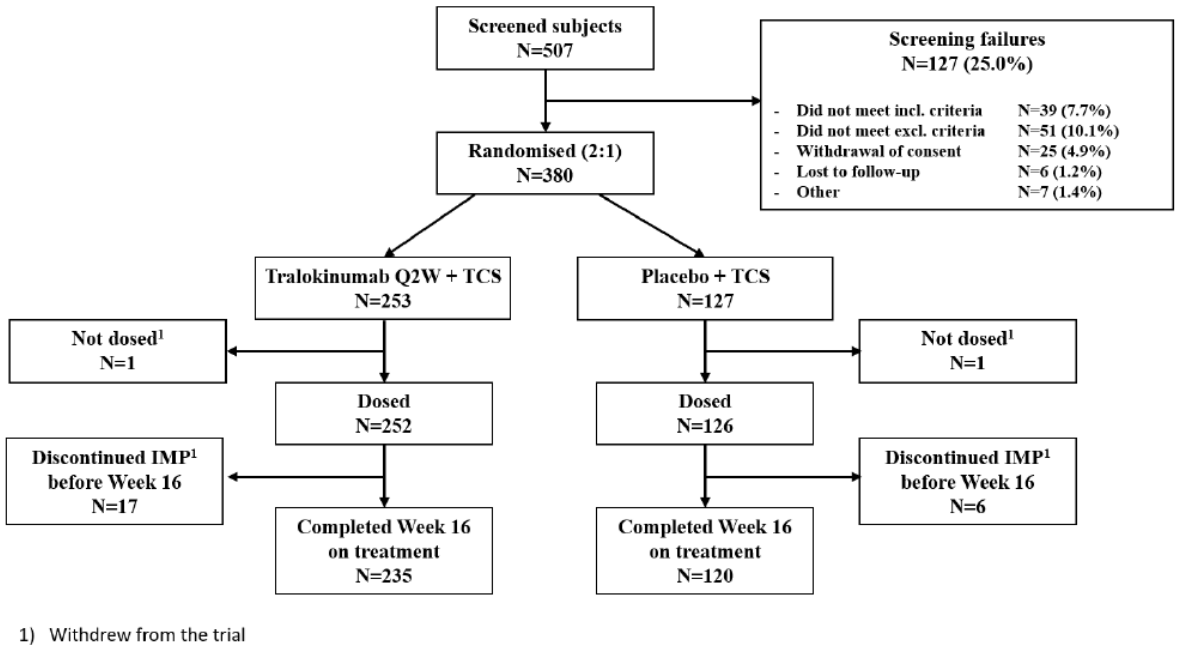
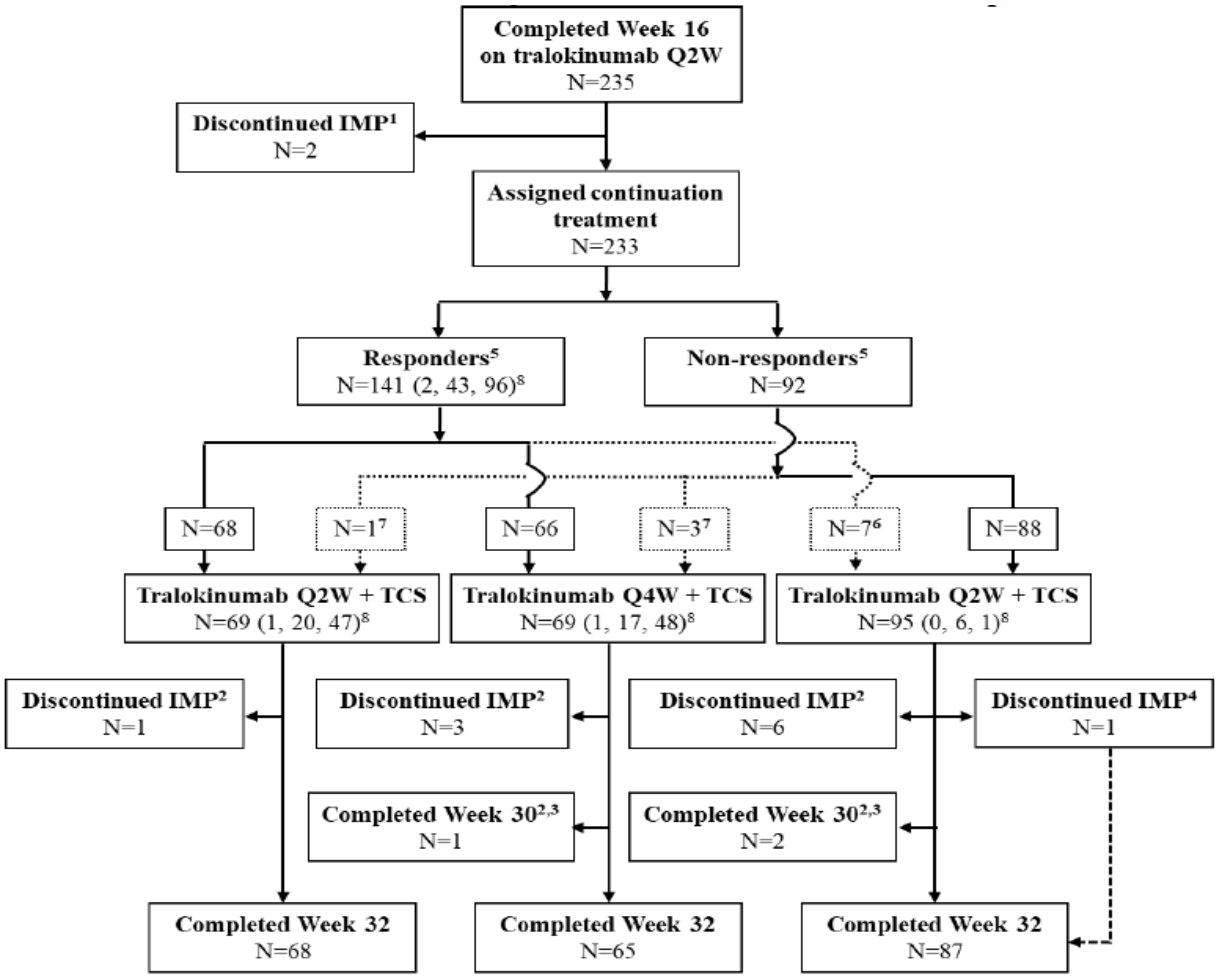


Figure 24 Participant flow in the initial treatment period, randomised subjects

Of the remaining 233 subjects, 141 subjects achieved a clinical response (tralokinumab+TCS responders) and 92 subjects did not achieve a clinical response (tralokinumab+TCS nonresponders) at Week 16 prior to receiving continuation treatment.



[1] 2 subjects discontinued IMP at Week 16 and withdrew from the trial at safety follow-up visit
[2] Withdrew from the trial
[3] Completed the continuation treatment (Week 30) but did not attend the Week 32 visit.
[4] Discontinued IMP but attended the Week 32 visit.
[5] A responder was defined as having IGA 0/1 or EASI75 at Week 16.
[6] Subjects were responders at Week 16 but were wrongly assigned continuation treatment.
[7] Subjects were non-responders at Week 16 but were wrongly re-randomised to continuation treatment.
[8] (IGA 0/1, EASI75, IGA 0/1 and EASI75) responders

Figure 25 Participant flow in the continuation treatment period, subject randomised to tralokinumab Q2W+TCS in the initial treatment period

Recruitment

Date of first subject first visit: 27-Feb-2018.

Date of last subject last visit (Week 32 data): 26-Jun-2019.

Conduct of the study

At the time of the data cut-off for the clinical study report (27-Jun-2019), the original protocol (04-October-2017, 0 subjects) had 3 global amendments.

The first amendment (15-Dec-2017), was a non-substantial amendment related to an operational change concerning the NIMP (TCS) and its handing out to the subjects.

In amendment 2 (10-Apr-2018), the major changes were related to the safety monitoring and disallowed medications.

The latest amendment took place in 29-August-2018, to introduce the possibility for eligible subjects in selected countries to participate to a long-term extension trial (conducted under a separate protocol [LP0162-1337, ECZTEND]) without completing the safety follow-up period in the present trial. A new ADA assay has been developed with improved tralokinumab tolerance. This means that the presence or absence of ADA can be determined in serum samples with tralokinumab present. Previously, this was not possible and therefore ADA sampling at the end of the 14-week off-treatment safety follow-up was originally required for the ADA evaluation. Thus, in selected countries, the new ADA assay allowed eligible subjects who have completed the treatment periods of the present trial to continue into the long-term extension trial without completing the safety follow-up period in the present trial. These subjects would have their safety follow-up period after end of treatment in the long-term extension trial.

196 major PDs were reported: 1 trial-level, 1 country-level, 16 site-level, and 178 subject-level major PDs. 4 major site-level PDs and 86 major subject-level PDs related to the assessment of safety and efficacy were reported.

1 major subject-level PD led to exclusion from the per protocol analysis set and 2 major subject-level PDs led to permanent discontinuation of IMP.

Baseline data

Demographics

Most of the subjects (93.7%) were 18–64 years at baseline. The remaining subjects (6.3%) were 65–84 years. The mean age at baseline was 39.1 years. In the tralokinumab Q2W+TCS group, men and women were equally distributed. In the placebo+TCS group, there was a higher proportion of men than women (66.1% vs 33.9% subjects). Most subjects were White (75.8% subjects) and not Hispanic or Latino (90.8% subjects) reflecting the regions and countries in which they were enrolled. 10.8% of patients were Asian and 9.2% were Black. There was a higher proportion of White subjects (80.2% vs 66.9% subjects) and a lower proportion of Asian subjects (6.7% vs 18.9% subjects) in the tralokinumab Q2W+TCS group than in the placebo+TCS group. The mean weight was 79.4 kg.

Baseline disease severity

In this study, 53.2% of patients had a baseline IGA score of 3, 46.3% of patients had a baseline IGA of 4, and 39.2 % of patients received prior systemic immunosuppressants. The baseline mean EASI score was 29.4, the baseline Worst Daily Pruritus NRS was 7.7, the baseline mean DLQI was 17.5, the baseline mean SCORAD score was 67.6, the baseline mean POEM score was 22.3 in the tralokinumab group and 22.4 in the placebo group.

The mean BSA at baseline was 48.1, age at onset of AD was 10.9 and duration of AD at baseline was 28.2.

Table 23 IGA, EASI, SCORAD, DLQI and Worst Daily Pruritus NRS (weekly average) at baseline: randomised subjects

	All randomised (n=380)	Tralokinumab Q2W + TCS (n=253)	Placebo + TCS (n=127)
Investigators Global Assessment			
N (%)	380 (100.0)	253 (100.0)	127 (100.0)
Moderate Disease	202 (53.2)	136 (53.8)	66 (52.0)
Severe Disease	176 (46.3)	116 (45.8)	60 (47.2)
Missing	2 (0.5)	1 (0.4)	1 (0.8)
EASI Score			
N	378	252	126
Mean (SD)	29.35 (12.25)	28.81 (11.97)	30.42 (12.78)
Median	25.50	24.65	26.50
Q1;Q3	(19.20;37.10)	(18.40;35.90)	(19.90;39.30)
Min;max	15.8;72.0	15.8;68.4	16.1;72.0
SCORAD Score			
N	378	252	126
Mean (SD)	67.59 (13.25)	66.95 (13.26)	68.86 (13.19)
Median	66.50	66.15	67.85
Q1;Q3	(57.90;77.60)	(57.55;76.25)	(59.40;79.00)
Min;max	35.1;102.6	37.5;102.6	35.1;101.0
DLQI Score			
N	375	250	125
Mean (SD)	17.45 (7.09)	17.58 (7.07)	17.19 (7.15)
Median	18.00	18.00	18.00
Q1;Q3	(12.00;23.00)	(12.00;23.00)	(12.00;23.00)
Min;max	1.0;30.0	1.0;30.0	2.0;30.0
Worst Pruritus (eDiary)			
N	377	251	126
Mean (SD)	7.74 (1.51)	7.67 (1.51)	7.86 (1.49)
Median	8.00	8.00	8.00
Q1;Q3	(6.57;8.86)	(6.57;8.71)	(7.00;9.00)
Min;max	3.0;10.0	3.0;10.0	4.4;10.0

Abbreviations: DLQI = Dermatology Life Quality Index; EASI = Eczema Area and

In line with the protocol requirements, almost all of the subjects had used topical corticosteroids (98.2% subjects). The use of any rescue medication was overall low in both treatment groups.

Numbers analysed

Table 24 Number analysed, initial treatment period (Week 0 to Week 16)

	Tralokinumab Q2W+TCS		Placebo+TCS	
	N	(%)	N	(%)
Randomised	253	(100)	127	(100)
Not dosed	1	(0.4)	1	(0.8)
Full analysis set	252	(99.6)	126	(99.2)
Safety analysis set	252	(99.6)	126	(99.2)
Per protocol analysis set	250	(98.8)	126	(99.2)

Abbreviations: N = number of subjects; Q2W = every 2 weeks; TCS = topical corticosteroid(s); % = percentage of subjects.

Table 25 Number analysed, continuation treatment period (Week 16 to Week 32)

	Week 16 Tralokinumab+TCS responders				Week 16 Tralokinumab+TCS non-responders		Week 16 Placebo+TCS non-responders		Week 16 Placebo+TCS responders	
	Tralokinumab Q2W+TCS		Tralokinumab Q4W+TCS		Tralokinumab Q2W+TCS		Tralokinumab Q2W+TCS		Placebo+TCS	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Assigned continuation treatment	69	(100)	69	(100)	95	(100)	79	(100)	41	(100)
Continuation treatment analysis set	69	(100)	69	(100)	95	(100)	79	(100)	41	(100)
Continuation treatment safety analysis set	69	(100)	69	(100)	95	(100)	79	(100)	41	(100)

Outcomes and estimation

Initial treatment period (Week 0 to Week 16)

Primary endpoints

- IGA 0/1 at Week 16

At Week 16, the proportion of IGA 0/1 responders was statistically significantly higher with tralokinumab Q2W+TCS than with placebo+TCS; the estimated treatment difference was 12.4% (p=0.015) with 38.9% responders in the tralokinumab Q2W+TCS group and 26.2% responders in the placebo+TCS group (primary analysis of the primary estimand).

Table 26 IGA 0/1 responders at Week 16 (primary endpoint): full analysis set

IGA 0/1 at Week 16	Tralokinumab Q2W+TCS (n=252) Responders (%)*	Placebo +TCS (n=126) Responders (%)*	Difference in percentage ** (95% CI)	p-value ***
Primary estimand: Composite				
Primary #	98/252 (38.9)	33/126 (26.2)	12.4 (2.9, 21.9)	0.015
Sensitivity 1 ##	98/252 (38.9)	33/126 (26.2)	12.4 (2.9, 21.9)	0.015
Sensitivity 2 ###	99/252 (39.3)	33/126 (26.2)	12.8 (3.3, 22.3)	0.012
Secondary estimand: Hypothetical				
Primary +	105.1/252 (41.7)	36.1/126 (28.6)	12.8 (2.7, 22.9)	0.013
Sensitivity ++	104.5/252 (41.5)	35.9/126 (28.5)	12.7 (2.6, 22.8)	0.013
Tertiary estimand: Treatment policy				
Primary §	98.0/252 (38.9)	33.0/126 (26.2)	12.4 (.,.)	
Sensitivity §§	98/252 (38.9)	33/126 (26.2)	12.4 (2.9, 21.9)	0.015

Q2W: Every 2 weeks, CI: Confidence interval, IGA: Investigators Global Assessment, n: number of subjects in analysis set, TCS: Topical corticosteroids.
* Mean across multiple imputations where applicable.
** Mantel-Haenszel risk difference, stratified by region and baseline IGA.
*** Single imputation analyses: Cochran-Mantel-Haenszel test, stratified by region and baseline IGA. Multiple imputation analyses: Combined inference from multiple Mantel-Haenszel risk differences and associated standard errors.
# Subjects who received rescue medication considered non-responders. Subjects with missing data at Week 16 imputed as non-responders.
Subjects who permanently discontinued investigational medicinal product [IMP] prior to Week 16 considered non-responders.
Missing data at Week 16 imputed using last observation carried forward [LOCF] for subjects who did not receive resuce medication and did not withdraw due to an adverse event [AE] or lack of efficacy.
\+ Data collected after permanent discontinuation of IMP or initiation of rescue medication not included. Multiple imputation of missing values at Week 16.
++ Placebo based imputation of missing values in active treatment group.
§ All data used as observed at Week 16. Multiple imputation of missing values. CI and p-value not calculated due to between-imputation variance being zero.
§§ Missing values at Week 16 imputed as non-responders.

An analysis based on the PP 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 FAS. The estimated treatment difference at Week 16 was 12.4% (95% CI: 2.8 to 21.9, p=0.015), with 38.8% responders in the tralokinumab Q2W+TCS group and 26.2% responders in the placebo+TCS group.

- EASI75 at Week 16

At Week 16, the proportion of EASI75 responders was statistically significantly higher with tralokinumab Q2W+TCS than with placebo+TCS; the estimated treatment difference was 20.2% (p<0.001) with 56.0% responders in the tralokinumab Q2W+TCS group and 35.7% responders in the placebo+TCS group (primary analysis of the primary estimand).

The primary analyses of the secondary and tertiary estimands, and all sensitivity analyses led to the same conclusion as the primary analysis of the primary estimand (p<0.001; all analyses).

Table 27 EASI75 responders at Week 16 (primary endpoint): full analysis set

EASI75 at Week 16	Tralokinumab Q2W +TCS (n=252) Responders(%)*	Placebo+TCS (n=126) Responders(%)*	Difference in percentage ** (95% CI)	p-value ***
Primary estimand: Composite				
Primary #	141/252(56.0)	45/126(35.7)	20.2 (9.8,30.6)	<0.001
Sensitivity 1 ##	140/252(55.6)	44/126(34.9)	20.6(10.2,30.9)	<0.001
Sensitivity 2 ###	143/252(56.7)	46/126(36.5)	20.2 (9.8,30.6)	<0.001
Secondary estimand: Hypothetical				
Primary +	147.4/252(58.5)	46.4/126(36.8)	21.6(10.9,32.3)	<0.001
Sensitivity ++	146.8/252(58.3)	46.3/126(36.7)	21.5(10.8,32.2)	<0.001
Tertiary estimand: Treatment policy				
Primary $	144.2/252(57.2)	45.8/126(36.3)	20.8(10.1,31.6)	<0.001
Sensitivity $$	141/252(56.0)	45/126(35.7)	20.2 (9.8,30.6)	<0.001

Q2W: Every 2 weeks, CI: Confidence interval, EASI75: At least 75% reduction in EASI score, EASI: Eczema Area and Severity Index, IGA: Investigators Global Assessment, n: number of subjects in analysis set, TCS: Topical corticosteroids.
* Mean across multiple imputations where applicable.
** Mantel-Haenszel risk difference, stratified by region and baseline IGA.
*** Single imputation analyses: Cochran-Mantel-Haenszel test, stratified by region and baseline IGA. Multiple imputation analyses: Combined inference from multiple Mantel-Haenszel risk differences and associated standard errors.
# Subjects who received rescue medication considered non-responders. Subjects with missing data at Week 16 imputed as non-responders.
Subjects who permanently discontinued investigational medicinal product [IMP] prior to Week 16 considered non-responders.
Missing data at Week 16 imputed using last observation carried forward [LOCF] for subjects who did not receive resuce medication and did not withdraw due to an adverse event [AE] or lack of efficacy.
+ Data collected after permanent discontinuation of IMP or initiation of rescue medication not included. Multiple imputation of missing values at Week 16.
++ Placebo based imputation of missing values in active treatment group.
$ All data used as observed at Week 16. Multiple imputation of missing values.
$$ Missing values at Week 16 imputed as non-responders.

An analysis based on the PP analysis set was repeated for the primary analysis of the primary estimand. The result based on PP analysis set supported the results based on the FAS. The estimated treatment difference at Week 16 was 20.2% (95% CI: 9.8 to 30.6, p<0.001), with 56.0% responders in the tralokinumab Q2W+TCS group and 35.7% responders in the placebo+TCS group.

Confirmatory secondary endpoints and estimands

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

At Week 16, the proportion of subjects with a reduction of Worst Daily Pruritus NRS (weekly average) of ≥4 was statistically significantly higher with tralokinumab Q2W+TCS than with placebo+TCS; the estimated treatment difference was 11.3% (p=0.037) with 45.4% responders in the tralokinumab Q2W+TCS group and 34.1% responders in the placebo+TCS group (primary analysis of the primary estimand).

Table 28 Reduction of Worst Daily Pruritus NRS (weekly average) of at least 4 from baseline to Week 16, based on subjects with a baseline Worst Daily Pruritus NRS (weekly average) of at least 4 (confirmatory secondary endpoint): full analysis set

Worst Daily Pruritus NRS (weekly average) reduction >=4 at Week 16	Tralokinumab Q2W+TCS (n=249) Responders(%)*	Placebo +TCS (n=126) Responders(%)*	Difference in percentage ** (95% CI)	p-value ***
Primary estimand: Composite				
Primary #	113/249(45.4)	43/126(34.1)	11.3 (0.9,21.6)	0.037
Sensitivity 1 ##	113/249(45.4)	43/126(34.1)	11.3 (0.9,21.6)	0.037
Sensitivity 2 ##	122/249(49.0)	46/126(36.5)	12.6 (2.1,23.0)	0.021
Secondary estimand: Hypothetical				
Primary +	128.4/249(51.6)	48.3/126(38.3)	13.3 (2.4,24.3)	0.017
Sensitivity ++	125.5/249(50.4)	48.5/126(38.5)	12.0 (1.2,22.9)	0.030
Tertiary estimand: Treatment policy				
Sensitivity $	115/249(46.2)	46/126(36.5)	9.7 (-0.7,20.2)	0.074

Q2W: Every 2 weeks, CI: Confidence interval, NRS: Numeric rating scale, IGA: Investigators Global Assessment, n: number of subjects in analysis set, TCS: Topical corticosteroids.
Based on subjects in full analysis set [FAS] with a baseline Pruritus NRS weekly average of at least 4.
* Mean across multiple imputations where applicable.
** Mantel-Haenszel risk difference, stratified by region and baseline IGA.
*** Single imputation analyses: Cochran-Mantel-Haenszel test, stratified by region and baseline IGA. Multiple imputation analyses: Combined inference from multiple Mantel-Haenszel risk differences and associated standard errors.
# Subjects who received rescue medication considered non-responders. Subjects with missing data at Week 16 imputed as non-responders.
Subjects who permanently discontinued investigational medicinal product [IMP] prior to Week 16 considered non-responders.
Missing data at Week 16 imputed using last observation carried forward [LOCF] for subjects who did not receive resuce medication and did not withdraw due to an adverse event [AE] or lack of efficacy.
+ Data collected after permanent discontinuation of IMP or initiation of rescue medication not included. Multiple imputation of missing values at Week 16.
++ Placebo based imputation of missing values in active treatment group.
§ Missing values at Week 16 imputed as non-responders.

- Change in SCORAD from baseline to Week 16

The adjusted mean change in SCORAD from baseline to Week 16 was statistically significantly higher with tralokinumab Q2W+TCS than with placebo+TCS indicating a greater improvement of AD disease symptoms in the tralokinumab Q2W+TCS group than in the placebo+TCS group. At Week 16, the estimated treatment difference was -10.9 ($p<0.001$) with an adjusted mean change of -37.7 in the tralokinumab Q2W+TCS group and -26.8 in the placebo+TCS group (primary analysis of the primary estimand).

Table 29 Change from baseline in SCORAD at Week 16 (confirmatory secondary endpoint): full analysis set

Change from baseline to Week 16 in SCORAD	Tralokinumab Q2W+TCS (n=252) Adjusted mean change (SE)	Placebo +TCS (n=126) Adjusted mean change (SE)	Difference (95% CI)	p-value
Primary estimand: Hypothetical				
Primary #	-37.7 (1.25)	-26.8 (1.80)	-10.9 (-15.2,-6.6)	<0.001
Sensitivity ##	-37.5 (1.27)	-26.7 (1.83)	-10.8 (-15.2,-6.5)	<0.001
Secondary estimand: Treatment policy				
Primary +	-37.4 (1.31)	-27.3 (1.85)	-10.1 (-14.5,-5.6)	<0.001
Sensitivity ++	-37.5 (1.49)	-27.3 (1.87)	-10.1 (-14.6,-5.6)	<0.001
Tertiary estimand: Composite				
Primary $	-37.1 (1.30)	-24.9 (1.83)	-12.1 (-16.5,-7.7)	<0.001

Q2W: Every 2 weeks, CI: Confidence interval, SE: Standard error, SCORAD: Scoring Atopic Dermatitis, IGA: Investigators Global Assessment, n: number of subjects in analysis set, TCS: Topical corticosteroids.
Data collected after permanent discontinuation of investigational medicinal product [IMP] or initiation of rescue medication not included. Repeated measurements model on post-baseline data: Change in SCORAD = Treatment*Week + [Baseline SCORAD]*Week + Region + Baseline IGA. In case of no post-baseline assessments before initiation of rescue medication, the Week 2, change is imputed as 0.
Analysis of covariance [ANCOVA] model at Week 16: Change in SCORAD = Treatment + Baseline SCORAD + Region + Baseline IGA. Multiple imputation of missing values at Week 16 based on data from placebo group.
+ All data used as observed at Week 16. Multiple imputation of missing values. ANCOVA model as above.
++ Placebo based imputation of missing values in active treatment group. ANCOVA model as above.
§ Worst observation carried forward for all subjects who received rescue medication. Multiple imputation of missing values for subjects who did not receive rescue medication. ANCOVA model as above.

- Change in DLQI score from baseline to Week 16

The adjusted mean change in DLQI from baseline to Week 16 was statistically significantly higher with tralokinumab Q2W+TCS than with placebo+TCS, indicating a greater improvement in subject's own perception of the impact of their AD on their HRQoL in the tralokinumab Q2W+TCS group than in the placebo+TCS group. At Week 16, the estimated treatment difference was -2.9 ($p<0.001$) with an adjusted mean change of -11.7 in the tralokinumab Q2W+TCS group and -8.8 in the placebo+TCS group.

Table 30 Change from baseline in DLQI at Week 16 (confirmatory secondary endpoint): full analysis set

Change from baseline to Week 16 in DLQI	Tralokinumab Q2W+TCS (n=252) Adjusted mean change (SE)	Placebo +TCS (n=126) Adjusted mean change (SE)	Difference (95% CI)	p-value
Primary estimand: Hypothetical				
Primary #	-11.7 (0.39)	-8.8 (0.56)	-2.9 (-4.3,-1.6)	<0.001
Sensitivity ##	-11.6 (0.40)	-8.8 (0.57)	-2.8 (-4.2,-1.5)	<0.001
Secondary estimand: Treatment policy				
Primary +	-11.8 (0.38)	-9.1 (0.59)	-2.8 (-4.1,-1.4)	<0.001
Sensitivity ++	-11.5 (0.50)	-9.1 (0.62)	-2.4 (-3.9,-1.0)	0.001
Tertiary estimand: Composite				
Primary $	-11.5 (0.42)	-8.1 (0.59)	-3.4 (-4.8,-2.0)	<0.001

Q2W: Every 2 weeks, CI: Confidence interval, SE: Standard error, DLQI: Dermatology Life Quality Index, IGA: Investigators Global Assessment, n: number of subjects in analysis set, TCS: Topical corticosteroids.
Data collected after permanent discontinuation of investigational medicinal product [IMP] or initiation of rescue medication not included. Repeated measurements model on post-baseline data: Change in DLQI = Treatment*Week + [Baseline DLQI]*Week + Region + Baseline IGA. In case of no post-baseline assessments before initiation of rescue medication, the Week 2, change is imputed as 0.
Analysis of covariance [ANCOVA] model at Week 16: Change in DLQI = Treatment + Baseline DLQI + Region + Baseline IGA. Multiple imputation of missing values at Week 16 based on data from placebo group.
+ All data used as observed at Week 16. Multiple imputation of missing values. ANCOVA model as above.
++ Placebo based imputation of missing values in active treatment group. ANCOVA model as above.
§ Worst observation carried forward for all subjects who received rescue medication. Multiple imputation of missing values for subjects who did not receive rescue medication. ANCOVA model as above.

Other secondary endpoints at Week 16

Other relevant endpoints results are presented inTable 31.

Table 31 Other endpoints results of Adtralza with concomitant TCS at Weeks 16 in ECZTRA 3

Combination therapy		
	ECZTRA 3 week 16	
	Placebo + TCS	**Adtralza 300 mg Q2W + TCS**
Patients randomised	126	252
Eczema-related sleep NRS, LS mean change from baseline (SE)[a)]	-3.1 (0.2)	-4.3§ (0.2)
POEM, LS mean change from baseline (SE)[a)]	-7.8 (0.7)	-11.8§ (0.5)
POEM (≥4-point improvement), % responders[b)]	59.3% (73/123)	78.4%§ (196/250)

LS: Least squares, SE: Standard error
If needed to control intolerable symptoms of atopic dermatitis, patients were permitted to receive rescue treatment at the discretion of the investigator.
a) Data after initiation of rescue medication or permanent discontinuation of treatment was excluded from the analyses.
b) Subjects who received rescue treatment or had missing data were treated as non-responders. The percentage is calculated relative to the number of subjects with POEM ≥4 at baseline.
§p<0.001

Continuation treatment period (Week 16 to Week 32)

- IGA 0/1 at Week 32 among subjects with IGA 0/1 at Week 16 after initial randomisation to tralokinumab Q2W+TCS

The proportion of subjects who maintained an IGA 0/1 response at Week 32 was slightly higher in the tralokinumab R/Q2W+TCS group than in the tralokinumab R/Q4W+TCS group

- 89.6% (43 of 48 subjects; 95% CI: 77.8 to 95.5) with tralokinumab R/Q2W+TCS.
- 77.6% (38 of 49 subjects; 95% CI: 64.1 to 87.0) with tralokinumab R/Q4W+TCS.

- IGA 0/1 at each scheduled assessment from Week 16 to Week 32 (all treatment groups)

Table 32 IGA 0/1 at each scheduled assessment from Week 16 to Week 32 (all treatment groups)

IGA 0/1	Week 16 Tralokinumab+TCS responders		Week 16 Tralokinumab+TCS non-responders	Week 16 Placebo+TCS non-responders	Week 16 Placebo+TCS responders
	Tralokinumab Q2W+TCS (n=69) Responders (%)[a]	Tralokinumab Q4W+TCS (n=69) Responders (%)[a]	Tralokinumab Q2W+TCS (n=95) Responders (%)[a]	Tralokinumab Q2W+TCS (n=79) Responders (%)[a]	Placebo+TCS (n=41) Responders (%)[a]
Week 16	48/69 (69.6)	49/69 (71.0)	1/95 (1.1)[b]	0/79 (0.0)	33/41 (80.5)
Week 18	49/69 (71.0)	40/69 (58.0)	5/95 (5.3)	4/79 (5.1)	30/41 (73.2)
Week 20	46/69 (66.7)	40/69 (58.0)	12/95 (12.6)	9/79 (11.4)	26/41 (63.4)
Week 22	47/69 (68.1)	44/69 (63.8)	14/95 (14.7)	13/79 (16.5)	25/41 (61.0)
Week 24	43/69 (62.3)	41/69 (59.4)	15/95 (15.8)	13/79 (16.5)	25/41 (61.0)
Week 26	45/69 (65.2)	43/69 (62.3)	19/95 (20.0)	18/79 (22.8)	25/41 (61.0)
Week 28	47/69 (68.1)	43/69 (62.3)	20/95 (21.1)	22/79 (27.8)	24/41 (58.5)
Week 30	46/69 (66.7)	43/69 (62.3)	24/95 (25.3)	22/79 (27.8)	27/41 (65.9)
Week 32	48/69 (69.6)	46/69 (66.7)	29/95 (30.5)	22/79 (27.8)	24/41 (58.5)

[a] Subjects who received rescue medication considered non-responders. Subjects with missing data at Week 32 imputed as non-responders. Responders and non-responders presented as treated.
[b] Tralokinumab+TCS responder assigned treatment in error.
Abbreviations: IGA = Investigator's Global Assessment; n = number of subjects in the analysis set; Q2W = every 2 weeks; Q4W = every 4 weeks; TCS = topical corticosteroids.
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- EASI75 at Week 32 among subjects with EASI75 at Week 16 after initial randomisation to tralokinumab Q2W+TCS

In both the tralokinumab R/Q2W+TCS and tralokinumab R/Q4W+TCS groups more than 90% subjects maintained the EASI75 response at Week 32.

- 92.5% (62 of 67 subjects; 95% CI: 83.7 to 96.8) with tralokinumab R/Q2W+TCS.
- 90.8% (59 of 65 subjects; 95% CI: 81.3 to 95.7) with tralokinumab R/Q4W+TCS.

- EASI75 at each scheduled assessment from Week 16 to Week 32 (all treatment groups)

Table 33 EASI75 responders by visit (all treatment groups), continuation treatment period: continuation treatment analysis set

EASI75	Week 16 Tralokinumab+TCS responders		Week 16 Tralokinumab+TCS non-responders	Week 16 Placebo+TCS non-responders	Week 16 Placebo+TCS responders
	Tralokinumab Q2W+TCS (n=69) Responders (%)[a]	Tralokinumab Q4W+TCS (n=69) Responders (%)[a]	Tralokinumab Q2W+TCS (n=95) Responders (%)[a]	Tralokinumab Q2W+TCS (n=79) Responders (%)[a]	Placebo+TCS (n=41 Responders (%)[a]
Week 16	67/69 (97.1)	65/69 (94.2)	7/95 (7.4)	4/79 (5.1)	40/41 (97.6)
Week 18	63/69 (91.3)	62/69 (89.9)	21/95 (22.1)	14/79 (17.7)	37/41 (90.2)
Week 20	62/69 (89.9)	64/69 (92.8)	35/95 (36.8)	26/79 (32.9)	35/41 (85.4)
Week 22	62/69 (89.9)	63/69 (91.3)	47/95 (49.5)	37/79 (46.8)	33/41 (80.5)
Week 24	64/69 (92.8)	63/69 (91.3)	47/95 (49.5)	38/79 (48.1)	34/41 (82.9)
Week 26	63/69 (91.3)	61/69 (88.4)	54/95 (56.8)	45/79 (57.0)	36/41 (87.8)
Week 28	63/69 (91.3)	62/69 (89.9)	52/95 (54.7)	40/79 (50.6)	34/41 (82.9)
Week 30	64/69 (92.8)	63/69 (91.3)	55/95 (57.9)	46/79 (58.2)	35/41 (85.4)
Week 32	64/69 (92.8)	60/69 (87.0)	53/95 (55.8)	42/79 (53.2)	32/41 (78.0)

[a] Subjects who received rescue medication considered non-responders. Subjects with missing data at Week 32 imputed as non-responders. Responders and non-responders presented as treated.
Abbreviations: EASI = Eczema Area and Severity Index; EASI75 = at least 75% reduction in EASI score; n = number of subjects in the analysis set; Q2W = every 2 weeks; Q4W = every 4 weeks; TCS = topical corticosteroids.
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Results of other secondary endpoints can be found in Table 36.

Ancillary analyses

ECZTRA 1 and 2

To assess the consistency in response rates for the primary endpoints across different subgroups, IGA 0/1 and EASI75 were analysed by the following subgroups for the monotherapy pool: age, sex, body weight, BMI, race, ethnicity, region, baseline scores of IGA, EASI, Pruritus NRS, and BSA, duration of AD, age of AD onset, previous use of systemic AD treatment, previous use of immunosuppressants, and relevant atopic disease history (asthma, food allergy, and hay fever). To support the interpretation of results for the monotherapy pool, subgroup analyses were also performed on a trial level.

Higher responder rates were observed in the tralokinumab group compared to the placebo group for the vast majority of the subgroups for both IGA 0/1 and EASI75. Treatment-by subgroup interactions (i.e. $p<0.05$) were observed within race, weight, region (US versus non- US), and age of AD onset for IGA 0/1 as well as race and weight for EASI75. These interactions were observed in conjunction with high placebo responses in categories within these subgroups.

ECZTRA 3

To assess the consistency in response rate of the primary endpoints in relation to disease severity at baseline and regions, the following subgroup analyses were performed of the primary estimand ('composite'):

- IGA 0/1 and EASI75 at Week 16 by baseline IGA.
- IGA 0/1 and EASI75 at Week 16 by region.

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

Within each treatment group, the proportion of IGA 0/1 responders was higher in subjects with a moderate disease at baseline compared to subjects with a severe disease at baseline; this was more pronounced in the placebo+TCS group than in the tralokinumab Q2W+TCS group. Irrespectively of disease severity at baseline, the proportion of IGA 0/1 responders was higher in the tralokinumab Q2W+TCS group than in the placebo+TCS group.

The corresponding subgroup analysis on EASI75 showed no marked difference in proportion of responders for subjects in the tralokinumab Q2W+TCS group whereas in the placebo+TCS group, the proportion of responders was higher in subjects with a moderate disease at baseline compared to subjects with a severe disease at baseline.

IGA 0/1 and EASI75 at Week 16 by region

Within each treatment group, there was no marked difference in proportion of responders between the regions North America and Europe with regards to both IGA 0/1 and EASI75.

Summary of main studies

The following tables summarise the efficacy results from the main studies 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 34 Tabular summary of efficacy for trial ECZTRA 1

Title: Tralokinumab monotherapy for moderate-to-severe atopic dermatitis ECZTRA 1 (Eczema Tralokinumab trial no. 1)		
Study identifier	LP0162-1325 2016-004200-65 NCT03131648	
Design	ECZTRA 1 was a phase 3 randomised, double-blind, placebo-controlled trial in adult subjects with moderate-to-severe atopic dermatitis (AD). The trial was conducted in Europe, Japan, and North America.	
	Duration of screening phase: Duration of initial phase: Duration of maintenance phase: Open-label phase: Safety follow-up phase:	2–6 weeks 16 weeks 36 weeks up to 36 Weeks 14 weeks
Hypothesis	Superiority	
Treatment groups in the initial treatment period	Tralokinumab Q2W	Tralokinumab loading dose of 600 mg at Week 0, then 300 mg every 2 weeks (Q2W) until Week 16: - N(randomised)=603 - N(dosed)=601
	Placebo	Placebo, same injection schedule as tralokinumab until Week 16: - N(randomised)=199 - N(dosed)=197
Treatment groups in the maintenance treatment period, subjects treated with tralokinumab in the initial treatment period who achieved a clinical response at	Tralokinumab Q2W	Tralokinumab 300 mg Q2W from Week 16: - N(re-randomised)=71 - N(dosed)=68
	Tralokinumab Q4W	Alternating treatment with tralokinumab 300 mg Q2W and placebo Q2W (Q4W) from Week 16: - N(re-randomised)=78 - N(dosed)=76

Week 16	Placebo		Placebo Q2W from Week 16: - N(re-randomised)=36 - N(dosed)=35
Treatment group in the maintenance treatment period, subjects treated with placebo in the initial treatment period who achieved a clinical response at Week 16	Placebo responders		Placebo Q2W from Week 16: - N(continued)=29 - N(dosed)=29
Treatment group in open-label treatment arm, subjects treated with tralokinumab or placebo in the initial treatment period who did not achieve a clinical response at Week 16	Tralokinumab Q2W + optional TCS		Tralokinumab Q2W+TCS from transfer at Week 16*: - N(assigned at Week 16)=506 - N(dosed)=506 *Subjects assigned to open-label treatment later than Week 16 are reflected in the maintenance treatment groups and consisted of 58 subjects, of which 57 subjects were dosed.
Endpoints and definitions, initial treatment period	Primary endpoints	IGA 0/1 at Week 16	IGA 0/1: IGA score of 0 (clear) or 1 (almost clear).
		EASI-75 at Week 16	EASI-75: at least 75% reduction in EASI score.
	Secondary endpoints	Change in SCORAD from baseline to Week 16	Change in Scoring Atopic Dermatitis (SCORAD) from baseline to Week 16.
		Reduction of Pruritus NRS ≥4-point from baseline to Week 16	Reduction of Worst Daily Pruritus NRS (weekly average) of at least 4 points from baseline to Week 16.
		Change in DLQI score from baseline to Week 16	Change in Dermatology Life Quality Index (DLQI) from baseline to Week 16.
	Additional secondary endpoints	EASI-50 at Week 16	At least 50% reduction in EASI score at Week 16.
		EASI-90 at Week 16	At least 90% reduction in EASI score at Week 16.
		% change in EASI score from baseline to Week 16	% change in EASI score from baseline to Week 16.
		SCORAD-50 at Week 16	At least 50% reduction in SCORAD at Week 16.
		% change in SCORAD from baseline to Week 16	% change in SCORAD score from baseline to Week 16.
		Change in Pruritus NRS from baseline to Week 16	Change in Worst Daily Pruritus NRS (weekly average) from baseline to Week 16.
		% change in Pruritus NRS from baseline to Week 16	% change in Worst Daily Pruritus NRS score from baseline to Week 16.
		Reduction in DLQI ≥4-point from baseline to	Reduction in DLQI ≥4 points from baseline to Week 16, among subjects with DLQI score ≥4 at baseline.

		Week 16	
	Other endpoints	Change in Sleep NRS from baseline to Week 16	Change in Eczema-related Sleep NRS (weekly average) from baseline to Week 16.
		Reduction in POEM (≥4-point reduction) from baseline to Week 16	Reduction in Patient Oriented Eczema Measure (POEM) (weekly average) ≥4 from baseline to Week 16, among subjects with POEM ≥4 at baseline.
		Change in POEM from baseline to Week 16	Change in POEM from baseline to Week 16.
		Change in SF-36, physical component from baseline to Week 16	Change in SF-36, physical component from baseline to Week 16.
		Change in SF-36, mental component from baseline to Week 16	Change in SF-36, mental component from baseline to Week 16.
		Skin colonisation of *S. aureus* at Week 16	Skin colonisation of *S. aureus* at Week 16 among subjects positive at baseline.
Endpoints and definitions, maintenance treatment period	Maintenance endpoints	IGA 0/1 at Week 52	IGA of 0/1 at Week 52 among subjects with IGA of 0/1 at Week 16 achieved without rescue medication after initial randomisation to tralokinumab.
		EASI-75 at Week 52	EASI-75 at Week 52 among subjects with EASI-75 at Week 16 achieved without rescue medication after initial randomisation to tralokinumab.
Endpoints and definitions, open-label treatment arm	Open-label endpoints	IGA 0/1 at Week 52	IGA of 0/1 at Week 52 among subjects initially randomised to tralokinumab and transferred to open-label treatment at Week 16.
		EASI-75 at Week 52	EASI-75 at Week 52 among subjects initially randomised to tralokinumab and transferred to open-label treatment at Week 16.
Multiplicity adjustment	To control the overall type 1 error rate, the primary analyses of the primary estimands for the primary and confirmatory secondary endpoints for the initial and maintenance treatment followed testing procedures with a testing hierarchy. The hypothesis relating to a specific endpoint could not be rejected unless all hypotheses relating to endpoints earlier in the hierarchy were also rejected. The testing hierarchy included the primary endpoints (IGA 0/1, and EASI-75 at Week 16), the secondary endpoints (change in SCORAD, change in DLQI, and reduction of ≥4-points in Pruritus NRS from baseline to Week 16), and the maintenance endpoints (IGA 0/1, and EASI-75 at Week 52).		
Database lock	18-Jul-2019 (DBL 2) including data released at DBL 1 (11-Apr-2019)		
Results and Analysis			
Analysis description	**Primary Analysis (16 weeks)**		
Analysis population and time point description	Full analysis set (FAS). FAS includes subjects randomised and exposed to investigational medicinal product (IMP). Initial treatment period (at Week 16 or change from baseline to Week 16). For the binary endpoints, the primary estimand ('composite') assessed the treatment difference in response rate after 16 weeks achieved without rescue medication, regardless of treatment discontinuation. For the continuous endpoints, the primary estimand ('hypothetical') assessed the treatment difference in change from baseline to Week 16, if all subjects adhered to the treatment regimen (did not discontinue IMP permanently and no rescue medication was made available before Week 16).		

Descriptive statistics and estimate variability	Treatment group	Tralokinumab Q2W	Placebo
	Number of subjects (FAS)	601	197
	IGA 0/1, % responders	15.8 (95/601)	7.1 (14/197)
	EASI-50, % responders	41.6 (250/601)	21.3 (42/197)
	EASI-75, % responders	25.0 (150/601)	12.7 (25/197)
	EASI-90, % responders	14.5 (87/601)	4.1 (8/197)
	EASI, LS mean % change from baseline (±SE)[3]	-51.3 (±1.9)	-28.5 (±3.7)
	SCORAD-50, % responders	26.0 (156/601)	11.7 (23/197)
	SCORAD, LS mean change from baseline (±SE)[3]	-25.2 (±0.9)	-14.7 (±1.8)
	SCORAD, LS mean % change from baseline (±SE)[3]	-36.7 (±1.4)	-20,3 (±2.7)
	Pruritus NRS (≥4-point reduction), % responders	20.0 (119/594)	10.3 (20/194)
	Pruritus NRS, LS mean change from baseline (±SE)[3]	-2.6 (±0.1)	-1.7 (±0.2)
	Pruritus NRS, LS mean % change from baseline (±SE)[3]	-33.6 (±1.6)	-21.9 (±3.1)
	DLQI (≥4-point reduction), % responders	44.6 (258/578)	31.6 (60/190)
	DLQI, LS mean change from baseline (±SE)[3]	-7.1 (±0.3)	-5.0 (±0.6)
	Sleep NRS, LS mean change from baseline (±SE)[3]	-2.6 (±0.1)	-1.9 (±0.2)
	POEM (>4-point reduction), % responders	43.0 (253/588)	18.0 (35/194)
	POEM, LS mean change from baseline (±SE)[3]	-7.6 (±0.4)	-3.0 (±0.7)
	SF-36 (physical), LS mean change from baseline (±SE)[3]	4.5 (±0.3)	2.9 (±0.6)
	SF-36 (mental), LS mean change from baseline (±SE)[3]	2.5 (±0.4)	0.3 (±0.8)
	Skin colonisation with *S. aureus*, median (n)[5] change from baseline (gene copy number/cm^2)	-670 (n=502)	-36 (n=166)
Effect estimate per comparison		Comparison groups	Tralokinumab Q2W, Placebo
	IGA 0/1, % responders	Treatment difference[1]	8.6
		95% CI[1]	4.1; 13.1
		P-value[2]	0.002
	EASI-50, % responders	Treatment difference[1]	20.1
		95% CI[1]	13.3; 26.8
		P-value[2]	<0.001
	EASI-75, % responders	Treatment difference[1]	12.1
		95% CI[1]	6.5; 17.7
		P-value[2]	<0.001
	EASI-90, % responders	Treatment difference[1]	10.3
		95% CI[1]	6.4; 14.1

		P-value[2]	<0.001
	EASI, LS mean % change from baseline	Treatment difference[3]	-22.8
		95% CI	-30.9; -14.7
		P-value	<0.001
	SCORAD-50, % responders	Treatment difference[1]	14.1
		95% CI[1]	8.6; 19.6
		P-value[2]	<0.001
	SCORAD, LS mean change from baseline	Treatment difference[3]	-10.4
		95% CI	-14.4; -6.5
		P-value	<0.001
	SCORAD, LS mean % change from baseline	Treatment difference[3]	-16.4
		95% CI	-22.4; -10.3
		P-value	<0.001
	Pruritus NRS (≥4-point reduction), % responders	Treatment difference[1]	9.7
		95% CI[1]	4.4; 15.0
		P-value[2]	0.002
	Pruritus NRS, LS mean change from baseline	Treatment difference[3]	-0.9
		95% CI	-1.4; -0.4
		P-value	<0.001
	Pruritus NRS, LS mean % change from baseline	Treatment difference[3]	-11.7
		95% CI	-18.5; -4.8
		P-value	0.0008
	DLQI (≥4-point reduction), % responders	Treatment difference[1]	13.0
		95% CI[1]	5.4; 20.5
		P-value[2]	0.001
	DLQI, LS mean change from baseline	Treatment difference[3]	-2.1
		95% CI	-3.4; -0.8
		P-value	0.002
	Sleep NRS, LS mean change from baseline	Treatment difference[3]	-0.7
		95% CI	-1.2; -0.2
		P-value	0.007
	POEM (>4-point reduction), % responders	Treatment difference[1]	25.0
		95% CI[1]	18.4; 31.5
		P-value[2]	<0.001
	POEM, LS mean change from baseline	Treatment difference[3]	-4.6
		95% CI	-6.0; -3.1
		P-value	<0.001
	SF-36 (physical), LS mean change from baseline	Treatment difference[3]	1.6
		95% CI	0.3; 2.8
		P-value	0.013
	SF-36 (mental), LS mean change from baseline	Treatment difference[3]	2.3
		95% CI	0.5; 4.0
		P-value	0.010
	Skin colonisation with *S. aureus*, relative reduction from baseline (gene copy number/cm^2)	Ratio[4]	0.09
		95% CI	0.054; 0.145
		P-value	<0.0001
	Analyses	[1]Mantel-Haenszel risk difference, stratified by region and baseline IGA. Subjects who received rescue treatment or had missing data were considered non-responders in the analysis. [2]Cochran-Mantel-Haenszel test, stratified by region and baseline IGA. [3]Mixed model for repeated measurements with fixed effect of treatment-by-week interaction, baseline score-by-week interaction, region and baseline IGA. Data after initiation of rescue medication or permanent discontinuation of treatment was excluded from the analyses.	

		[4]The ratio between the treatment groups in relative reductions of S. aureus colonisation from baseline to Week 16 was assessed by a t-test of changes in log-transformed values. 5Number of subjects (n) with an available change from baseline.		
Analysis population and time point description	Maintenance analysis set: Subjects who received tralokinumab in the initial treatment period and who were re-randomised and exposed to maintenance treatment. Maintenance treatment period (at Week 52). Primary estimand ('composite') assessed the treatment difference in response rate after 52 weeks achieved without rescue medication and without transfer to open-label treatment.			
Descriptive statistics and estimate variability	Treatment group	Tralokinumab Q2W	Tralokinumab Q4W	Placebo
	Number of subjects[4]	39	36	19
	IGA 0/1, % responders	51.3 (20/39)	38.9 (14/36)	47.4 (9/19)
	Number of subjects[5]	47	57	30
	EASI-75, % responders	59.6 (28/47)	49.1 (28/57)	33.3 (10/30)
Effect estimate per comparison		Comparison groups	Tralokinumab Q2W, Placebo	Tralokinumab Q4W, Placebo
	IGA 0/1, % responders	Treatment	6.0	-9.5
		95% CI[6]	-21.8; 33.7	-37.1; 18.0
		P-value[7]	0.68	0.50
	EASI-75, % responders	Treatment difference[6]	21.2	11.7
		95% CI[6]	-0.2; 42.6	-8.7; 32.0
		P-value[7]	0.056	0.27
	Analyses	[4]Subjects with IGA 0/1 at Week 16 achieved without rescue medication. [5]Subjects with EASI75 at Week 16 achieved without rescue medication. [6]Mantel-Haenszel risk difference compared to placebo, stratified by region. [7]Cochran-Mantel-Haenszel test, stratified by region.		
Analysis population and time point description	Open-label analysis set: Subjects initially randomised to tralokinumab Q2W who were transferred to open-label treatment at Week 16. Open-label treatment (at Week 52).			
Descriptive statistics and estimate variability	Treatment group		Tralokinumab Q2W + optional TCS	
	Subject number		360	
	IGA 0/1, % responders[8]		20.8 (75/360)	
	EASI-75, % responders[8]		46.1 (166/360)	
	Analyses	[8]Subjects who had missing data were considered non-responders in the analysis.		

Table 35 Tabular summary of efficacy for trial ECZTRA 2

Title: Tralokinumab monotherapy for moderate-to-severe atopic dermatitis ECZTRA 2 (Eczema Tralokinumab trial no. 2)			
Study identifier	LP0162-1326 2016-004201-13 NCT03160885		
Design	This was a phase 3 randomised, double-blind, placebo-controlled trial in adult subjects with moderate-to-severe atopic dermatitis (AD). The trial was conducted in Europe, Korea, Australia and North America.		
	Duration of screening phase: Duration of initial phase: Duration of maintenance phase: Open-label phase: Safety follow-up phase:		2–6 weeks 16 weeks 36 weeks up to 36 Weeks 14 weeks
Hypothesis	Superiority		
Treatment groups in the initial treatment period	Tralokinumab Q2W		Tralokinumab loading dose of 600 mg at Week 0, then 300 mg every 2 weeks (Q2W) until Week 16: - N(randomised)=593 - N(dosed)=591
	Placebo		Placebo, same injection schedule as tralokinumab until Week 16: - N(randomised)=201 - N(dosed)=201
Treatment groups in the maintenance treatment period, subjects treated with tralokinumab in the initial treatment period who achieved a clinical response at Week 16	Tralokinumab Q2W		Tralokinumab 300 mg Q2W from Week 16: - N(re-randomised)=91 - N(dosed)=91
	Tralokinumab Q4W		Alternating treatment with tralokinumab 300 mg Q2W and placebo Q2W (Q4W) from Week 16: - N(re-randomised)=90 - N(dosed)=89
	Placebo		Placebo Q2W from Week 16: - N(re-randomised)=46 - N(dosed)=46
Treatment group in the maintenance treatment period, subjects treated with placebo in the initial treatment period who achieved a clinical response at Week 16	Placebo responders		Placebo Q2W from Week 16: - N(continued)=31 - N(dosed)=31
Treatment group in open-label treatment arm, subjects treated with tralokinumab or placebo in the initial treatment period who did not achieve a clinical response at Week 16	Tralokinumab Q2W + optional TCS		Tralokinumab Q2W+TCS from transfer at Week 16*: - N(assigned at Week 16)=471 - N(dosed)=469 *Subjects assigned to open-label treatment later than Week 16 are reflected in the maintenance treatment groups and consisted of 89 subjects (all subjects were dosed).
Endpoints and definitions, initial treatment period	Primary endpoints	IGA 0/1 at Week 16	IGA 0/1: IGA score of 0 (clear) or 1 (almost clear).
		EASI-75 at Week 16	EASI-75: at least 75% reduction in EASI score.
	Secondary endpoints	Change in SCORAD from baseline to Week 16	Change in Scoring Atopic Dermatitis (SCORAD) from baseline to Week 16.

		Reduction of Pruritus NRS ≥4-point from baseline to Week 16	Reduction of Worst Daily Pruritus NRS (weekly average) of at least 4 points from baseline to Week 16.
		Change in DLQI score from baseline to Week 16	Change in Dermatology Life Quality Index (DLQI) from baseline to Week 16.
	Additional secondary endpoints	EASI-50 at Week 16	At least 50% reduction in EASI score at Week 16.
		EASI-90 at Week 16	At least 90% reduction in EASI score at Week 16.
		% change in EASI score from baseline to Week 16	% change in EASI score from baseline to Week 16.
		SCORAD-50 at Week 16	At least 50% reduction in SCORAD at Week 16.
		% change in SCORAD from baseline to Week 16	% change in SCORAD score from baseline to Week 16.
		Change in Pruritus NRS from baseline to Week 16	Change in Worst Daily Pruritus NRS (weekly average) from baseline to Week 16.
		% change in Pruritus NRS from baseline to Week 16	% change in Worst Daily Pruritus NRS score from baseline to Week 16.
	Other endpoints	Change in Sleep NRS from baseline to Week 16	Change in Eczema-related Sleep NRS (weekly average) from baseline to Week 16.
		Reduction in POEM (≥4-point reduction) from baseline to Week 16	Reduction in Patient Oriented Eczema Measure (POEM) (weekly average) ≥4 from baseline to Week 16, among subjects with POEM ≥4 at baseline.
		Change in POEM from baseline to Week 16	Change in POEM from baseline to Week 16.
		Change in SF-36, physical component from baseline to Week 16	Change in SF-36, physical component from baseline to Week 16.
		Change in SF-36, mental component from baseline to Week 16	Change in SF-36, mental component from baseline to Week 16.
Endpoints and definitions, maintenance treatment period	Maintenance endpoints	IGA 0/1 at Week 52	IGA of 0/1 at Week 52 among subjects with IGA of 0/1 at Week 16 achieved without rescue medication after initial randomisation to tralokinumab.
		EASI-75 at Week 52	EASI-75 at Week 52 among subjects with EASI-75 at Week 16 achieved without rescue medication after initial randomisation to tralokinumab.

Endpoints and definitions, open-label treatment arm	Open-label endpoints	IGA 0/1 at Week 52	IGA of 0/1 at Week 52 among subjects initially randomised to tralokinumab and transferred to open-label treatment at Week 16.
		EASI-75 at Week 52	EASI-75 at Week 52 among subjects initially randomised to tralokinumab and transferred to open-label treatment at Week 16.
Multiplicity adjustment	To control the overall type 1 error rate, the primary analyses of the primary estimands for the primary and confirmatory secondary endpoints for the initial and maintenance treatment followed testing procedures with a testing hierarchy. The hypothesis relating to a specific endpoint could not be rejected unless all hypotheses relating to endpoints earlier in the hierarchy were also rejected. The testing hierarchy included the primary endpoints (IGA 0/1, and EASI-75 at Week 16), the secondary endpoints (change in SCORAD, change in DLQI, and reduction of ≥4-points in Pruritus NRS from baseline to Week 16), and the maintenance endpoints (IGA 0/1, and EASI-75 at Week 52).		
Database lock	14-Aug-2019 (DBL 2) including data released at DBL 1 (09-May-2019)		
Results and Analysis			
Analysis description	**Primary Analysis (16 weeks)**		
Analysis population and time point description	Full analysis set (FAS). FAS includes subjects randomised and exposed to investigational medicinal product (IMP). Initial treatment period (at Week 16 or change from baseline to Week 16). For the binary endpoints, the primary estimand ('composite') assessed the treatment difference in response rate after 16 weeks achieved without rescue medication, regardless of treatment discontinuation. For the continuous endpoints, the primary estimand ('hypothetical') assessed the treatment difference in change from baseline to Week 16, if all subjects adhered to the treatment regimen (did not discontinue IMP permanently and no rescue medication was made available before Week 16).		
Descriptive statistics and estimate variability	Treatment group	Tralokinumab Q2W	Placebo
	Number of subjects (FAS)	591	201
	IGA 0/1, % responders	22.2 (131/591)	10.9 (22/201)
	EASI-50, % responders	49.9 (295/591)	20.4 (41/201)
	EASI-75, % responders	33.2 (196/591)	11.4 (23/201)
	EASI-90, % responders	18.3 (108/591)	5.5 (11/201)
	EASI, LS mean % change from baseline (±SE)	-56.5 (±1.8)	-22.2 (±3.5)
	SCORAD-50, % responders	33.5 (198/591)	14.4 (29/201)
	SCORAD, LS mean change from baseline (±SE)	-28.1 (±0.9)	-14.0 (±1.8)
	SCORAD, LS mean % change from baseline (±SE)	-40.6 (±1.3)	-20.6 (±2.6)
	Pruritus NRS (≥4-point reduction), % responders	25.0 (144/575)	9.5 (19/200)
	Pruritus NRS, LS mean change from baseline (±SE)	-2.9 (±0.1)	-1.6 (±0.2)
	Pruritus NRS, LS mean % change from baseline (±SE)	-37.0 (±1.4)	-21.0 (±2.8)
	DLQI (≥4-point reduction), % responders	56.3 (325/577)	27.3 (54/198)
	DLQI, LS mean change from baseline (±SE)	-8.8 (±0.3)	-4.9 (±0.6)

	Sleep NRS, LS mean change from baseline (±SE)	-2.9 (±0.1)	-1.5 (±0.2)
	POEM (>4-point reduction), % responders	54.4 (319/586)	22.1 (44/199)
	POEM, LS mean change from baseline (±SE)	-8.8 (±0.3)	-3.7 (±0.7)
	SF-36 (physical), LS mean change from baseline (±SE)	5.8 (±0.3)	3.2 (±0.6)
	SF-36 (mental), LS mean change from baseline (±SE)	3.5 (±0.4)	0.5 (±0.8)
Effect estimate per comparison		Comparison groups	Tralokinumab Q2W, Placebo
	IGA 0/1, % responders	Treatment difference[1]	11.1
		95% CI[1]	5.8; 16.4
		P-value[2]	<0.001
	EASI-50, % responders	Treatment difference[1]	29.3
		95% CI[1]	22.5; 36.1
		P-value[2]	<0.001
	EASI-75, % responders	Treatment difference[1]	21.6
		95% CI[1]	15.8; 27.3
		P-value[2]	<0.001
	EASI-90, % responders	Treatment difference[1]	12.7
		95% CI[1]	8.3; 17.0
		P-value[2]	<0.001
	EASI, LS mean % change from baseline[3]	Treatment difference[3]	-34.3
		95% CI	-42.0; -26.6
		P-value	<0.001
	SCORAD-50, % responders	Treatment difference[1]	18.9
		95% CI[1]	12.8; 25.1
		P-value[2]	<0.001
	SCORAD, LS mean change from baseline[3]	Treatment difference[3]	-14.0
		95% CI	-18.0; -10.1
		P-value	<0.001
	SCORAD, LS mean % change from baseline[3]	Treatment difference[3]	20.0
		95% CI	-25.8; -14.2
		P-value	<0.001
	Pruritus NRS (≥4-point reduction), % responders	Treatment difference[1]	15.6
		95% CI[1]	10.3; 20.9
		P-value[2]	<0.001
	Pruritus NRS, LS mean change from baseline[3]	Treatment difference[3]	-1.3
		95% CI	-1.7; -0.8
		P-value	<0.001
	Pruritus NRS, LS mean % change from baseline[3]	Treatment difference[3]	-15.9
		95% CI	-22.1; -9.8
		P-value	<0.0001
	DLQI (≥4-point reduction), % responders	Treatment difference[1]	28.9
		95% CI[1]	21.4; 36.3
		P-value[2]	<0.001
	DLQI, LS mean change from baseline[3]	Treatment difference[3]	-3.9
		95% CI	-5.2; -2.6
		P-value	<0.001
	Sleep NRS, LS mean change from baseline[3]	Treatment difference[3]	-1.4
		95% CI	-1.9; -0.9

		P-value		<0.001
	POEM (>4-point reduction), % responders	Treatment difference[1]		32.1
		95% CI[1]		25.2; 39.1
		P-value[2]		<0.001
	POEM, LS mean change from baseline[3]	Treatment difference[3]		-5.1
		95% CI		-6.5; -3.6
		P-value		<0.001
	SF-36 (physical), LS mean change from baseline[3]	Treatment difference[3]		2.6
		95% CI		1.4; 3.9
		P-value		<0.001
	SF-36 (mental), LS mean change from baseline[3]difference[6]	Treatment difference[3]		3.0
		95% CI		1.3; 4.7
		P-value		<0.001
	Analyses	[1]Mantel-Haenszel risk difference, stratified by region and baseline IGA. Subjects who received rescue treatment or had missing data were considered non-responders in the analysis. [2]Cochran-Mantel-Haenszel test, stratified by region and baseline IGA. [3]Mixed model for repeated measurements with fixed effect of treatment-by-week interaction, baseline score-by-week interaction, region and baseline IGA. Data after initiation of rescue medication or permanent discontinuation of treatment was excluded from the analyses.		
Analysis population and time point description	Maintenance analysis set: Subjects who receive tralokinumab in the initial treatment period and who are re-randomised and exposed to maintenance treatment. Maintenance treatment period (at Week 52). Primary estimand ('composite') assessed the treatment difference in response rate after 52 weeks achieved without rescue medication and without transfer to open-label treatment.			
Descriptive statistics and estimate variability	Treatment group	Tralokinumab Q2W	Tralokinumab Q4W	Placebo
	Number of subjects[4]	54	49	28
	IGA 0/1, % responders	59.3 (32/54)	44.9 (22/49)	25.0 (7/28)
	Number of subjects[5]	77	74	42
	EASI-75, % responders	55.8 (43/77)	51.4 (38/74)	21.4 (9/42)
Effect estimate per comparison		Comparison groups	Tralokinumab Q2W, Placebo	Tralokinumab Q4W, Placebo
	IGA 0/1, % responders	Treatment difference[6]	34.1	19.9
		95% CI[6]	13.4; 54.9	-1.2; 40.9
		P-value[7]	0.004	0.084
	EASI-75, % responders	Treatment difference[6]	33.7	30.0
		95% CI[6]	17.3; 50.0	13.7; 46.4
		P-value[7]	<0.001	0.001
	Analyses	[4]Subjects with IGA 0/1 at Week 16 achieved without rescue medication. [5]Subjects with EASI75 at Week 16 achieved without rescue medication. [6]Mantel-Haenszel risk difference compared to placebo, stratified by region. [7]Cochran-Mantel-Haenszel test, stratified by region.		
Analysis population and time point description	Open-label analysis set: Subjects initially randomised to tralokinumab Q2W who were transferred to open-label treatment at Week 16. Open-label treatment (at Week 52).			
Descriptive statistics and estimate	Treatment group		Tralokinumab Q2W + optional TCS	

variability	Subject number		326
	IGA 0/1, % responders[8]		19.3 (63/326)
	EASI-75, % responders[8]		39.3 (128/326)
	Analyses	[8]Subjects who had missing data were considered non-responders in the analysis.	

Table 36 Tabular summary of efficacy for trial ECZTRA 3

Title: Tralokinumab in combination with topical corticosteroids for moderate-to-severe atopic dermatitis ECZTRA 3 (ECZema TRAlokinumab trial no. 3)			
Study identifier	LP0162-1339 2017-002065-21 NCT03363854		
Design	This was a phase 3 randomised, double-blind, placebo-controlled trial to confirm the efficacy and safety of tralokinumab administered on a background of TCS therapy in adult subjects with moderate-to-severe atopic dermatitis (AD). The trial was conducted in Europe and North America.		
	Duration of screening phase: Duration of initial phase: Duration of continuation phase: Safety follow-up phase:	2–6 weeks 16 weeks 16 weeks 14 weeks	
Hypothesis	Superiority		
Treatment groups in the initial treatment period	Tralokinumab Q2W+TCS	Tralokinumab loading dose of 600 mg at Week 0, then 300 mg every 2 weeks (Q2W) until Week 16, in combination with TCS: - N(randomised)=253 - N(dosed)=252	
	Placebo+TCS	Placebo, same injection schedule as tralokinumab until Week 16, in combination with TCS: - N(randomised)=127 - N(dosed)=126	
Treatment groups in the continuation treatment period, for subjects treated with tralokinumab in the initial treatment period	Tralokinumab Q2W+TCS, tralokinumab responders (TR)	Tralokinumab 300 mg Q2W until Week 32, in combination with TCS: - N(re-randomised)=69 (of which 1 was a non-responder randomised in error)	
	Tralokinumab Q4W+TCS, TR	Tralokinumab 300 mg Q4W (alternating treatment with tralokinumab 300 mg Q2W and placebo Q2W) until Week 32, in combination with TCS: - N(re-randomised)=69 (of which 3 were non-responders randomised in error)	
	Tralokinumab Q2W+TCS, tralokinumab non-responders (TNR)	Tralokinumab 300 mg Q2W until Week 32, in combination with TCS: - N(allocated)=95 (of which 7 were responders randomised in error)	
Treatment groups in the continuation treatment period, for subjects treated with placebo in the initial treatment period	Placebo+TCS, placebo responders	Placebo Q2W until Week 32, in combination with TCS: - N(continued)=41	
	Tralokinumab Q2W+TCS, placebo non-responders (PNR)	Tralokinumab 300 mg Q2W until Week 32, in combination with TCS: - N(allocated)=79 (of which 4 were placebo responders allocated in error)	
Endpoints and definitions, initial treatment period	Primary endpoints: IGA 0/1 at Week 16	IGA 0/1: IGA score of 0 (clear) or 1 (almost clear).	
	Primary endpoints: EASI-75 at Week 16	EASI-75: at least 75% reduction in EASI score.	

	Secondary endpoints	Change in SCORAD from baseline to Week 16	Change in Scoring Atopic Dermatitis (SCORAD) from baseline to Week 16.
		Reduction of Pruritus NRS ≥4-point from baseline to Week 16	Reduction of Worst Daily Pruritus NRS (weekly average) of at least 4 points from baseline to Week 16.
		Change in DLQI score from baseline to Week 16	Change in Dermatology Life Quality Index (DLQI) from baseline to Week 16.
	Additional secondary endpoints	EASI-50 at Week 16	At least 50% reduction in EASI score at Week 16.
		EASI-90 at Week 16	At least 90% reduction in EASI score at Week 16.
		% change in EASI score from baseline to Week 16	% change in EASI score from baseline to Week 16.
		SCORAD-50 at Week 16	At least 50% reduction in SCORAD at Week 16.
		% change in SCORAD from baseline to Week 16	% change in SCORAD score from baseline to Week 16.
		Change in Pruritus NRS from baseline to Week 16	Change in Worst Daily Pruritus NRS (weekly average) from baseline to Week 16.
		% change in Pruritus NRS from baseline to Week 16	% change in Worst Daily Pruritus NRS score from baseline to Week 16.
		Reduction in DLQI ≥4-point from baseline to Week 16	Reduction in DLQI ≥4 points from baseline to Week 16, among subjects with DLQI score ≥4 at baseline.
	Other endpoints	Change in Sleep NRS from baseline to Week 16	Change in Eczema-related Sleep NRS (weekly average) from baseline to Week 16.
		Reduction in POEM (≥4-point reduction) from baseline to Week 16	Reduction in Patient Oriented Eczema Measure (POEM) (weekly average) ≥4 from baseline to Week 16, among subjects with POEM ≥4 at baseline.
		Change in POEM from baseline to Week 16	Change in POEM from baseline to Week 16.
Endpoints and definitions, continuation treatment period	Maintenance endpoints in the continuation period	IGA 0/1 at Week 32	IGA of 0/1 at Week 32 among subjects with IGA of 0/1 at Week 16 achieved without rescue medication after initial randomisation to tralokinumab.
		EASI-75 at Week 32	EASI-75 at Week 32 among subjects with EASI-75 at Week 16 achieved without rescue medication after initial randomisation to tralokinumab.
	Other endpoints in the continuation period	EASI-50 at Week 32	At least 50% reduction in EASI score at Week 32.
		EASI-90 at Week 32	At least 90% reduction in EASI score at Week 32.

		% change in EASI score from baseline to Week 32	% change in EASI score from baseline to Week 32.
		% change in SCORAD from baseline to Week 32	% change in SCORAD from baseline to Week 32 among subjects re-randomised at Week 16.
		Reduction in Pruritus NRS (≥4-point reduction) from baseline to Week 32	Reduction in the Worst Daily Pruritus NRS (weekly average) ≥4 from baseline to Week 32.
		Change in Pruritus NRS from baseline to Week 32	Change in Worst Daily Pruritus NRS from baseline to Week 32.
		Reduction in DLQI score (>4-point reduction) from baseline to Week 32	Reduction DLQI score (weekly average) ≥4 from baseline to Week 32.
		Change in DLQI score from baseline to Week 32	Change in DLQI from baseline to Week 32.
		Change in Sleep NRS) from baseline to Week 32	Change in Eczema-related Sleep NRS from baseline to Week 32.
		Reduction in POEM (>4-point reduction) from baseline to Week 32	Reduction POEM (weekly average) ≥4 from baseline to Week 32.
		Change in POEM from baseline to Week 32	Change in POEM from baseline to Week 32.
Multiplicity adjustment	The overall type 1 error rate for the primary analysis of the primary estimands for the primary and confirmatory secondary endpoints was protected by a combination of hierarchical testing and Holm-Bonferroni multiplicity adjustment. The hypothesis relating to a specific endpoint could not be rejected unless all hypotheses relating to endpoints earlier in the hierarchy were also rejected. The testing hierarchy included the primary endpoints (IGA 0/1, and EASI-75 at Week 16) and the secondary endpoints (change in SCORAD, change in DLQI, and reduction of ≥4-points in Pruritus NRS from baseline to Week 16).		
Database lock	27-Jun-2019 (DBL 1)		
Results and Analysis			
Analysis description	**Primary Analysis (16 weeks)**		
Analysis population and time point description	Full analysis set (FAS). FAS includes subjects randomised and exposed to investigational medicinal product (IMP). Initial treatment period (at Week 16 or change from baseline to Week 16). For the binary endpoints, the primary estimand ('composite') assessed the treatment difference in response rate after 16 weeks achieved without rescue medication, regardless of treatment discontinuation. For the continuous endpoints, the primary estimand ('hypothetical') assessed the treatment difference in change from baseline to Week 16, if all subjects adhered to the treatment regimen (did not discontinue IMP permanently and no rescue medication was made available before Week 16).		
Descriptive	Treatment group	Tralokinumab	Placebo+TCS

statistics and estimate variability		Q2W+TCS	
	Number of subjects (FAS)	252	126
	IGA 0/1, % responders	38.9 (98/252)	26.2 (33/126)
	EASI-50, % responders	79.4 (200/252)	57.9 (73/126)
	EASI-75, % responders	56.0 (141/252)	35.7 (45/126)
	EASI-90, % responders	32.9 (83/252)	21.4 (27/126)
	EASI, LS mean % change from baseline (±SE)[3]	-71.3 (±2.2)	-55.3 (±3.2)
	SCORAD-50, % responders	61.1 (154/252)	38.1 (48/126)
	SCORAD, LS mean change from baseline (±SE)[3]	-37.7 (±1.3)	-26.8 (±1.8)
	SCORAD, LS mean % change from baseline (±SE)[3]	-55.9 (±1.8)	-40.0 (±2.6)
	Pruritus NRS (≥4-point reduction), % responders	45.4 (113/249)	34.1 (43/126)
	Pruritus NRS, LS mean change from baseline (±SE)[3]	-4.1 (±0.2)	-2.9 (±0.2)
	Pruritus NRS, LS mean % change from baseline (±SE)[3]	-52.4 (±2.0)	-37.4 (±2.9)
	DLQI (≥4-point reduction), % responders	83.5 (207/248)	65.9 (81/123)
	DLQI, LS mean change from baseline (±SE)[3]	-11.7 (±0.4)	-8.8 (±0.6)
	Sleep NRS, LS mean change from baseline (±SE)[3]	-4.3 (±0.2)	-3.1 (±0.2)
	POEM (>4-point reduction), % responders	78.4 (196/250)	59.3 (73/123)
	POEM, LS mean change from baseline (±SE)[3]	-11.8 (±0.5)	-7.8 (±0.7)
Effect estimate per comparison		Comparison groups	Tralokinumab Q2W+TCS, Placebo+TCS
	IGA 0/1, % responders	Treatment difference[1]	12.4
		95% CI[1]	2.9; 21.9
		P-value[2]	0.015
	EASI-50, % responders	Treatment difference[1]	21.3
		95% CI[1]	11.3; 31.3
		P-value[2]	<0.001
	EASI-75, % responders	Treatment difference[1]	20.2
		95% CI[1]	9.8; 30.6
		P-value[2]	<0.001
	EASI-90, % responders	Treatment difference[1]	11.4
		95% CI[1]	2.1; 20.7
		P-value[2]	<0.022
	EASI, LS mean % change from baseline	Treatment difference[3]	-16.0
		95% CI	-23.7; -8.3
		P-value	<0.001
	SCORAD-50, % responders	Treatment difference[1]	22.9

		95% CI[1]	12.4; 33.3
		P-value[2]	<0.001
	SCORAD, LS mean change from baseline	Treatment difference[3]	-10.9
		95% CI	-15.2; -6.6
		P-value	<0.001
	SCORAD, LS mean % change from baseline	Treatment difference[3]	-15.9
		95% CI	-22.2; -9.5
		P-value	<0.001
	Pruritus NRS (≥4-point reduction), % responders	Treatment difference[1]	11.3
		95% CI[1]	0.9; 21.6
		P-value[2]	0.037
	Pruritus NRS, LS mean change from baseline	Treatment difference[3]	-1.2
		95% CI	-1.7; -0.7
		P-value	<0.001
	Pruritus NRS, LS mean % change from baseline	Treatment difference[3]	-15.1
		95% CI	-22.0; -8.2
		P-value	<0.0001
	DLQI (≥4-point reduction), % responders	Treatment difference[1]	17.6
		95% CI[1]	8.0; 27.1
		P-value[2]	<0.001
	DLQI, LS mean change from baseline	Treatment difference[3]	-2.9
		95% CI	-4.3; -1.6
		P-value	<0.001
	Sleep NRS, LS mean change from baseline (SE)	Treatment difference[3]	-1.3
		95% CI	-1.8; -0.8
		P-value	<0.001
	POEM (>4-point reduction), % responders	Treatment difference[1]	19.1
		95% CI[1]	8.9; 29.2
		P-value[2]	<0.001
	POEM, LS mean change from baseline (SE)	Treatment difference[3]	-4.0
		95% CI	-5.6; -2.4
		P-value	<0.001
	Analyses	[1]Mantel-Haenszel risk difference, stratified by region and baseline IGA. Subjects who received rescue treatment or had missing data were considered non-responders in the analysis. [2]Cochran-Mantel-Haenszel test, stratified by region and baseline IGA. [3]Mixed model for repeated measurements with fixed effect of treatment-by-week interaction, baseline score-by-week interaction, region and baseline IGA. Data after initiation of rescue medication or permanent discontinuation of treatment was excluded from the analyses.	

Analysis population and time point description	Continuation analysis set (CAS): Subjects who receive tralokinumab in the initial treatment period and who are re-randomised/allocated to continuation treatment. Continuation treatment period (at Week 32 or change from baseline to Week 32).			
Descriptive statistics and estimate variability	Treatment group	Tralokinumab responders at Week 16		Tralokinumab non-responders at Week 16[4]
		Tralokinumab Q2W+TCS	Tralokinumab Q4W+TCS	Tralokinumab Q2W+TCS
		Week 32	Week 32	Week 32
	Number of subjects	48	49	95
	IGA 0/1, % responders	89.6[1] (43/48)	77.6[1] (38/49)	30.5 (29/95)
	Number of subjects	67	65	95
	EASI-75, %	92.5[2]	90.8[2]	55.8

	responders	(62/67)		(59/65)		(53/95)	
	Treatment group	Tralokinumab responders at Week 16[3]				Tralokinumab non-responders[4] at Week 16	
		Tralokinumab Q2W+TCS		Tralokinumab Q4W+TCS		Tralokinumab Q2W+TCS	
		Week 16	Week 32	Week 16	Week 32	Week 16	Week 32
	Number of subjects (CAS)	69		69		95	
	EASI-50, % resp.	100.0	98.6	97.1	91.3	63.2	76.8
	EASI-90, % resp.	58.0	72.5	60.9	63.8	1.1	34.7
	EASI, LS mean % change from baseline[4] (±SE)	-90.5 (±2.7)	-93.2 (±2.3)	-89.3 (±2.7)	-91.5 (±2.3)	-46.9 (±2.4)	-73.5 (±2.0)
	SCORAD, LS mean % change from baseline[4] (±SE)	-73.2 (±2.1)	-79.2 (±2.5)	-72.3 (±2.1)	-73.3 (±2.5)	-32.7 (±1.8)	-54.5 (±2.2)
	Pruritus NRS, (≥4-point reduction), % resp.	63.2	70.6	64.2	61.2	27.4	38.9
	Pruritus NRS, LS mean change from baseline[4] (±SE)	-5.0 (±0.2)	-5.4 (±0.2)	-4.6 (±0.2)	-4.9 (±0.2)	-3.0 (±0.2)	-3.7 (±0.2)
	Treatment group	Tralokinumab responders at Week 16[3]					
		Tralokinumab Q2W+TCS		Tralokinumab Q4W+TCS			
		Week 16	Week 32	Week 16	Week 32		
	Subject number (CAS)	69		69			
	DLQI (≥4-point reduction), % resp.	98.5 (65/66)	89.4 (59/66)	100.0 (68/68)	83.8 (57/68)		
	DLQI, LS mean change from baseline[5] (±SE)	-14.0 (±0.6)	-14.6 (±0.6)	-13.9 (±0.6)	-13.7 (±0.6)		
	Sleep NRS, LS mean change from baseline[5] (±SE)	-5.2 (±0.2)	-5.5 (±0.2)	-4.8 (±0.2)	-5.2 (±0.3)		
	POEM (≥4-point reduction), % resp.	89.7 (61/68)	88.2 (60/68)	94.1 (64/68)	83.8 (57/68)		
	POEM, LS mean change from baseline[5] (±SE)	-15.2 (±0.7)	-15.6 (±0.7)	-14.1 (±0.7)	-13.9 (±0.8)		
	Analyses	[1]Analysis included tralokinumab responders with IGA 0/1 at Week 16. Subjects who received rescue treatment or had missing data were treated as non-responders. The percentage is calculated relative to the number of subjects with response at week 16. [2]Analysis included tralokinumab responders with EASI-75 at Week 16. Subjects who received rescue treatment or had missing data were treated as non-responders. The percentage is calculated relative to the number of subjects with response at week 16. [3]Responders at Week16 were defined as subjects achieving either IGA 0/1 and/or EASI-75. Subjects who received rescue treatment or had missing data were considered non-responders in the analyses. [4]Non-responders at Week 16 were defined as subjects who did not achieve either IGA 0/1 or EASI-75. [5]Data after initiation of rescue medication or permanent discontinuation of treatment was excluded from the analyses. Mixed model for repeated measures was used with fixed effect of treatment-by-week interaction, baseline score-by-week interaction, region and baseline IGA.						

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

The integrated analyses were presented as pooled data from ECZTRA 1+2 (monotherapy pool), as these trials had identical design up to Week 52. The monotherapy pool can therefore give more precise

estimates of the treatment effect of tralokinumab. The results of the primary endpoints for the monotherapy pool are provided in Figure 15 and Figure 17.

In addition, subgroup analyses for the ECZTRA 1+2 studies (monotherapy pool) are presented in section Ancillary analyses.

Clinical studies in special populations

No additional studies in special populations were performed. The pivotal studies only recruited adult patients. Only a small percentage of patients (<7%) enrolled to studies were elderly i.e. >65 year of age. Information in relation to patients with renal or hepatic impairment is included in the popPK analyses described in the PK section of this assessment report.

Supportive studies

ECZTRA 5

This was a phase 2 randomised, double-blind, placebo-controlled trial in adult subjects with moderate-to-severe AD. The trial was conducted in North America.

The primary objective is presented in section 'PD interactions with other medicinal products or substances'.

The secondary objective was to evaluate efficacy of tralokinumab concomitantly administered with vaccines.

The proportions of subjects achieving positive anti-tetanus response and positive anti-meningococcal response in tralokinumab-treated subjects (91.9% and 86.0%) were non-inferior to those in placebo-treated subjects (96.1% and 84.2%), indicating that tralokinumab does not impair the immune response to non-live vaccines.

The proportion of IGA 0/1 responders at Week 16 was higher in the tralokinumab group (31.1%) compared to the placebo group (19.4%) based on the primary analysis of the composite estimand (treatment difference 11.4%, p=0.049).

The proportion of EASI75 responders at Week 16 was higher in the tralokinumab group (49.1%) compared to the placebo group (36.1%) based on the primary analysis of the composite estimand; however, the treatment difference (12.7%) did not reach statistical significance (p=0.057).

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy of tralokinumab as monotherapy and with concomitant TCS was evaluated in three pivotal randomised, double-blind, placebo-controlled studies (ECZTRA 1, ECZTRA 2 and ECZTRA 3) in 1 976 patients 18 years of age and older with moderate to severe AD defined by IGA score of 3 or 4 (moderate or severe), an EASI score of ≥ 16 at baseline, and a minimum BSA involvement of ≥ 10%. Eligible patients enrolled into the three studies had previous inadequate response to topical medication. The eligibility criteria were adequate for the inclusion of patients with moderate to severe AD and comparable across the clinical studies.

The ECZTRA 1 and 2 studies, which were almost identical in design, consisted of a screening period (2 to 6 weeks), an initial treatment period of 16 weeks and a maintenance treatment period of 36 weeks for subjects who obtained a clinical response at Week 16. The design of ECZTRA 3 study was similar with the exception that the duration of the maintenance period was shorter (16 weeks instead of 36 weeks). In addition, tralokinumab responders were not re-randomised to placebo.

An active comparator trial was not performed although it was recommended during the scientific advice (EMA/CHMP/SAWP/590489/2016) that such trial would be beneficial in the positioning of this biologic in the therapeutic armamentarium for AD. The applicant stated that at the time of initiating of the phase 3 clinical trials none of the systemic immunosuppressants (cyclosporine, methotrexate, azathioprine, and mycophenolate mofetil) where globally approved for AD and therefore could not conduct such study. Despite the lack of an active comparator trial, the design of the studies is considered acceptable by CHMP to characterise the efficacy profile of tralokinumab in AD.

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

In the monotherapy studies, subjects who achieved a clinical response at Week 16 were eligible to continue maintenance treatment and were re-randomised in a 2:2:1 ratio to receive Q2W injections of either 300 mg tralokinumab, Q4W injections of 300 mg tralokinumab or placebo for the following 36 weeks. Responders to placebo at Week 16 continued to receive placebo in the maintenance treatment period. In the combination study, subjects randomised to tralokinumab + TCS in the initial treatment period who had a clinical response at Week 16 were re-randomised into the continuation treatment period in a 1:1 ratio to tralokinumab 300 mg Q2W +TCS or tralokinumab 300 mg Q4W + TCS. Patients with the response to placebo + TCS in the initial treatment period continued to receive placebo + TCS in the continuation treatment period (Week 16 to Week 32).

The 300 mg dose was selected based on the results of the phase 2b dose finding study (D2213C00001) which assessed the efficacy of tralokinumab Q2W at doses of 45, 150 and 300 mg. Although no significant differences were evident between the 150 mg and 300 mg tralokinumab treatment groups, in general it is accepted that the data suggest an additive benefit of the higher dose and that they are supportive for the chosen 300 mg dose and Q2W posology brought forward for further efficacy investigation in the pivotal phase 3 studies. This was endorsed in scientific advice received from the CHMP/SAWP (EMA/CHMP/SAWP/590489/2016). During the evaluation, the applicant clarified that the decision for not investigating higher doses was based on the small differences in EASI score changes from the baseline at Week 12 between 150mg Q2W and 300 mg Q2W (mean difference from placebo group -4.4 and -4.9, respectively). They further stated that PK-PD simulation data demonstrated only a minor effect of increasing dose frequency to once weekly in terms of EASI-75 responders. This justification was accepted by CHMP.

The primary endpoints in the three pivotal studies were the proportion of patients with an IGA 0 or 1 ("clear" or "almost clear") and a reduction of a least 75% in EASI (EASI-75) from baseline to Week 16. These primary endpoints are considered adequate and in line with the CHMP scientific advice recommendation.

There was a number of secondary endpoints in those studies; however, only few were included under multiplicity adjustment: change in SCORAD, reduction of Worst Daily Pruritus NRS (weekly average) ≥4 and change in DLQI score from baseline to Week 16. In the ECZTRA 1 and 2 studies, two endpoints for the maintenance treatment period were also included in the confirmatory testing strategy. These endpoints were: IGA of 0/1 at Week 52 among subjects with IGA of 0/1 at Week 16 achieved without rescue medication after initial randomisation to tralokinumab and EASI75 at Week 52 among subjects

with EASI75 at Week 16 achieved without rescue medication after initial randomisation to tralokinumab. In the ECZTRA 3 study subjects received the last dose of tralokinumab or placebo at week 30. However, continuation treatment period endpoints were not included in the confirmatory testing strategy and only descriptive statistics were provided for these endpoints. Other endpoints included change from baseline to week 16 in POEM, at least 4-point improvement in POEM, and Eczema-related Sleep NRS.

Overall the chosen primary and secondary endpoints are considered adequate by CHMP.

Across all studies, there was a considerable number of major protocol deviations and about 25 % of subjects screened to these studies were affected (see sections on 'Conduct of the study'). In addition, two-study sites were terminated due to concerns about GCP non-compliance and data integrity.

The first clinical site based in the US affected one completed clinical trial (ECZTRA 3/LP0162-1339) and three ongoing clinical trials (ECZTRA 6, ECZTEND, ECZTRA 4). 12 subjects were randomised to the ECZTRA 3 study at this site. A post-hoc sensitivity analysis excluding these 12 subjects was performed with no impact on the efficacy and safety. The second terminated site affected the ECZTRA 2 study. 20 subjects were randomised at this site (12 subjects to tralokinumab Q2W and 8 subjects to placebo). The 20 subjects were included in the efficacy analysis in line with the intention-to-treat principle. Post-hoc calculations showed that exclusion of the 20 subjects from the analysis would not have a significant impact on the efficacy and safety results. Further, in the ECZTRA studies, a per protocol analysis set did not exclude all patients with major protocol deviations. There were uncertainties as to how these protocol deviations influenced the study results in terms of both efficacy and safety. The applicant stated that the per protocol analysis set was pre-defined based on selected key disease-defining inclusion criteria. Missing efficacy data were handled according to the pre-defined estimand strategies and approaches for handling of missing data, including sensitivity analyses. Based on the responses received from the applicant in relation to protocol deviations it is not expected that exclusion criteria violation has caused biased in the efficacy results, or had effects on individual safety and safety conclusions. In addition, the criteria used to define the per protocol population are considered as justified. Overall, it is not expected that PDs has had a significant effect on the results and benefit/risk balance.

Efficacy data and additional analyses

Primary endpoints

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) were met in all three pivotal studies.

In the primary analysis of the primary estimand in ECZTRA 1 and ECZTRA 2 studies, the proportion of patients with IGA 0 or 1 at Week 16 was higher in the tralokinumab Q2W groups (15.8% and 22.2% respectively) than in the placebo groups (7.1% and 10.9% respectively) with p=0.002 for ECZTRA 1 and <0.001 for ECZTRA 2. The proportion of patients with EASI-75 at Week 16 was also higher in the tralokinumab Q2W groups (25.0 % for ECZTRA 1 and 33.2 % for ECZTRA 2) as compared to the placebo groups (12.7% for ECZTRA 1 and 11.4% ECZTRA 2). The observed differences were statistically significant (p<0.0001 for each).

Similar results were observed in ECZTRA 3, the proportion of patients with IGA 0 or 1 at Week 16 was higher in the tralokinumab Q2W+TCS group (38.9%) than in the placebo +TCS group (26.2%) (p=0.015) and the proportion of patients with EASI-75 at Week 16 was also higher in the tralokinumab Q2W+TCS group (56.0%) than in the placebo +TCS group (35.7%) (p<0.001).

Albeit statistically significant, the effect size in the monotherapy trials was considered small by CHMP.

The majority of patients enrolled to the monotherapy studies did not respond to treatment. Only 34 % of patients in ECZTRA 1 study and 41% of patients in ECZTRA 2 who completed 16 weeks of treatment on tralokinumab were considered as tralokinumab responders (defined as IGA of 0 or 1 **or** EASI-75 score from baseline) and they were re-randomised (2:2:1) to the maintenance treatment. In addition, only 26% of subjects in ECZTRA 1 and 36 % in ECZTRA 2 achieved this clinical response without the use of rescue medications. This may have been the result of inadequate efficacy.

The applicant was asked to discuss this poor response to tralokinumab and whether any additional selection criteria could be used to increase likelihood of response or identify patients more likely to respond to tralokinumab treatment. The relevant review was performed by the applicant. Subgroup analyses of IGA 0/1 and EASI75 in the monotherapy pool, did not identify any baseline characteristics or selection criteria that were predictive of achieving either of these outcomes at Week 16. Similarly, a post-hoc subgroup analysis of EASI50 did not identify any baseline characteristics or selection criteria that were predictive of achieving a clinically relevant reduction in EASI score at Week 16.

In the ECZTRA 3 study which investigated tralokinumab given in combination with TCS more patients responded to treatment i.e. 60% of the subjects tested.

The applicant further discussed the clinical relevance and clinical significance of the treatment effect of tralokinumab both as monotherapy and in combination with TCS.

It was indicated that IGA 0/1 and EASI-75 are chosen as preferred primary outcomes in clinical trials, however they have outcomes with a lower threshold and that secondary endpoints (such as IGA 0/1/2 and EASI50) are considered more informative for the evaluation of the clinically relevant effects. In the clinical studies, the effect size was indeed increased with lower thresholds which are considered relevant for clinical practice. However, CHMP considered that the increase in efficacy even after consideration of minimum clinically important differences (MCIDs) instead of primary and secondary outcomes is still modest. Nevertheless, this treatment effect can still be considered as clinically relevant in patients who have not responded to other treatment options. Therefore, the benefit of tralokinumab used as monotherapy, or in combination with TCS is considered to be demonstrated. As better efficacy results were reported in the TCS combination trial (ECZTRA 3) as compared to monotherapy studies the following statement has been included in sections 4.2 the SmPC: "The use of topical corticosteroids, when appropriate, may provide an additional effect to the overall efficacy of tralokinumab".

Disease severity and assessment at baseline were comparable between the monotherapy studies but with a slightly lower disease severity in ECZTRA 3 compared to the other trials. This may have affected the efficacy results in favour of the combination therapy. Therefore, based on subgroup analysis provided by the applicant, it is assumed that differences in treatment response between ECZTRA 3 and monotherapy trials are mainly due to additional TCS therapy and not related to differences in baseline characteristics.

Secondary endpoints

For the initial treatment period the secondary endpoints results supported the effects seen in the primary endpoints. For secondary endpoints including those under multiplicity adjustment (i.e. a reduction of Worst Daily Pruritus NRS of ≥4 from baseline, change in SCORAD from baseline to Week 16-ECZTRA 1, Change in DLQI score from baseline to Week 16) statistically significantly better results were reported in patients receiving tralokinumab as compared to patients on placebo.

Reduction of Worst Daily Pruritus NRS (weekly average) ≥4 from baseline, which can be considered as a clinically relevant patient-reported outcome from a clinical viewpoint, has shown small favourable effects (12.6% and 11.3%) in monotherapy and combination therapy trials respectively.

Consistent results were reported for the primary, secondary and tertiary estimands and all sensitivity analyses, although 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. Hence, the primary estimand sensitivity analysis using placebo-based imputation in which data collected after permanent discontinuation of IMP or after initiation of rescue medication were assumed to resemble data from subjects in the placebo arm who did not discontinue treatment/receive rescue medication is reported in section 5.1 of the SmPC.

In both monotherapy studies (ECZTRA 1 and ECZTRA 2) and in the concomitant TCS study (ECZTRA 3) tralokinumab improved patient-reported symptoms of AD, as measured by POEM, and the impact of AD on sleep, as measured by Eczema-related sleep NRS, at Week 16 compared to placebo. A higher proportion of patients treated with tralokinumab had clinically meaningful reductions in POEM, (defined as at least 4 point improvement) from baseline to week 16 compared to placebo. These endpoints were not included in the confirmatory testing strategy.

Long-term efficacy

As discussed in studies ECZTRA 1 and 2, in the maintenance treatment period, 2 secondary endpoints were under confirmatory strategy: IGA 0/1 at Week 52 among subjects with IGA 0/1 at Week 16 and EASI75 at Week 52 among subjects with EASI75 at Week 16, whereas in ECZTRA 3 only descriptive statistics were provided for these endpoints.

The number of patients enrolled to the maintenance periods was smaller than planned due to the fact that only tralokinumab or placebo responders were transitioned to these periods and the percentage of responders was smaller than expected. Therefore, the maintenance period endpoints were likely to be underpowered.

In the ECZTRA 1 study, percentage of responders in the Q2W group was only slightly higher when compared to placebo and the difference was not statistically significant (6.0% difference for IGA 0/1 at Week 52 endpoint and 21.2% difference for EASI75 at Week 52 endpoint in the primary analysis of the composite estimand).

Better results were reported in ECZTRA 2 study. In this study, 34.1% more responders for IGA 0/1 at the Week 52 endpoint (p=0.004) and 33.7 % more responders for EASI75 at the Week 52 endpoint (p=<0.001) were seen in the Q2W group as compared to the placebo group on the risk difference scale.

In the ECZTRA 3 study, subjects received the last dose of tralokinumab or placebo at week 30. The continuation treatment period endpoints were not included in the confirmatory testing strategy and only descriptive statistics were used for these endpoints. For this reason, no firm conclusion can be drawn in relation to long term efficacy from this study. It seems, however, that the majority of responders at Week 16 maintain their response up to week 32.

An additional long-term data will be provided in the ongoing PASS (ECZTEND).

Q4W dose regimen

In ECZTRA 1 and 2 studies, the Q4W dose regimen was found to be less efficacious as compared to the Q2W regimen. For the Q4W dose regimen, a statistically (nominally) significant difference was only reported for the EASI75 at Week 52 endpoint in the ECZTRA 2 study (within endpoints under multiplicity adjustment). Lower efficacy as compared to the Q2W regimen was also observed for the vast majority of other endpoints investigated in these studies.

Based on the results on IGA0/1 and EASI75 in the monotherapy pool, efficacy of maintenance treatment with tralokinumab in the Q4W dosing regimen can be accepted, however the probability of maintaining clear or almost clear skin may be lower with every fourth week dosing. This is reflected in section 4.2 of the SmPC.

In addition, for some subpopulation of patients tapering the dose to every fourth week may not appropriate. The reduced exposure in patients with a high body weight (>100 kg), coupled with the reduced exposure with the Q4W regimen, suggests that the Q4W regimen may not be appropriate for patients with a high body weight. This is reflected in section 4.2 of the SmPC.

In ECZTRA 3, the continuation treatment period endpoints were not included in the confirmatory testing strategy and only descriptive statistics were used for these endpoints. For this reason, no firm conclusion can be drawn in relation to the efficacy of the Q4W dose regimen based on the results of ECZTRA 3 study.

The applicant was asked to clarify if there were any cases of rebound i.e. a significant worsening of the disease after stopping the treatment with tralokinumab. The applicant identified two 2 out of 132 who met or were on their way to meeting the conservative EASI-based rebound criterion. However, as none of these subjects reported worse itch or a higher impact of their AD on sleep compared to baseline the applicant did not consider any subjects to have experienced a true rebound effect following discontinuation of tralokinumab. It is agreed that information on patients with potential rebound effects is limited and therefore it is agreed to not include this information in the SmPC. However, these cases should be monitored in the post-marketing setting.

Open-label treatment

Subjects who did not achieve a clinical response at Week 16 as well as subjects who did not maintain adequate clinical response during the maintenance treatment period were transferred to open-label treatment (i.e. tralokinumab 300 mg Q2W plus optional use of TCS). In this open label arm, the percentage of responders increased overtime.

Time to event analysis in open label treatment period, did not illustrate a plateau pattern in cumulative probability of response for neither monotherapy nor combination therapy trials. This indicated that some patients may still benefit from treatment after 52/32 weeks. Optimal time point for therapy discontinuation in non-responders is inconclusive, provided the results of time to event analysis.

Therefore, consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment. Some patients with initial partial response may subsequently improve further with continued treatment every other week beyond 16 weeks. This statement has been included in section 4.2 of the SmPC.

2.5.4. Conclusions on the clinical efficacy

A significant better efficacy compared to placebo was demonstrated for tralokinumab as monotherapy or in combination with TCS in AD patients who are insufficiently controlled with topical therapies alone. Therefore, the CHMP endorsed the proposed dose of 300 mg every other week (Q2W) with a loading dose of 600 mg on day 1 and the dose of 300 mg every fourth week (Q4W) for patients who achieve clear or almost clear skin after 16 weeks of treatment.

2.6. Clinical safety

The safety of tralokinumab was evaluated in a pool of 5 completed randomised, double-blind, placebo-controlled studies in patients with moderate-to-severe AD including the three phase 3 studies

(ECZTRA 1, ECZTRA 2, and ECZTRA 3), the dose-ranging study (D2213C00001) and the vaccine-response study (ECZTRA 5).

Safety data were also submitted from 4 ongoing supportive studies with tralokinumab including the phase 3 long-term safety and efficacy study in adult subjects previously participating in the ECZTRA trials (ECZTEND), the drug-drug interaction study (ECZTRA 4) and 2 additional phase 3 study (ECZTRA 7, ECTRA 6). Data from 17 clinical trials in asthma, ulcerative colitis (UC), and idiopathic pulmonary fibrosis (IPF) is also available as supporting data only.

For the integrated safety analysis, four data pools were assembled: AD pool (ECZTRA1, ECZTRA2, ECZTRA3, ECZTRA5 and D2213C00001), asthma pool (STRATOS 1 and 2, CD-RI-CAT- 354-1049), exposure pool (all completed trials with tralokinumab across all indications) (Figure 26).

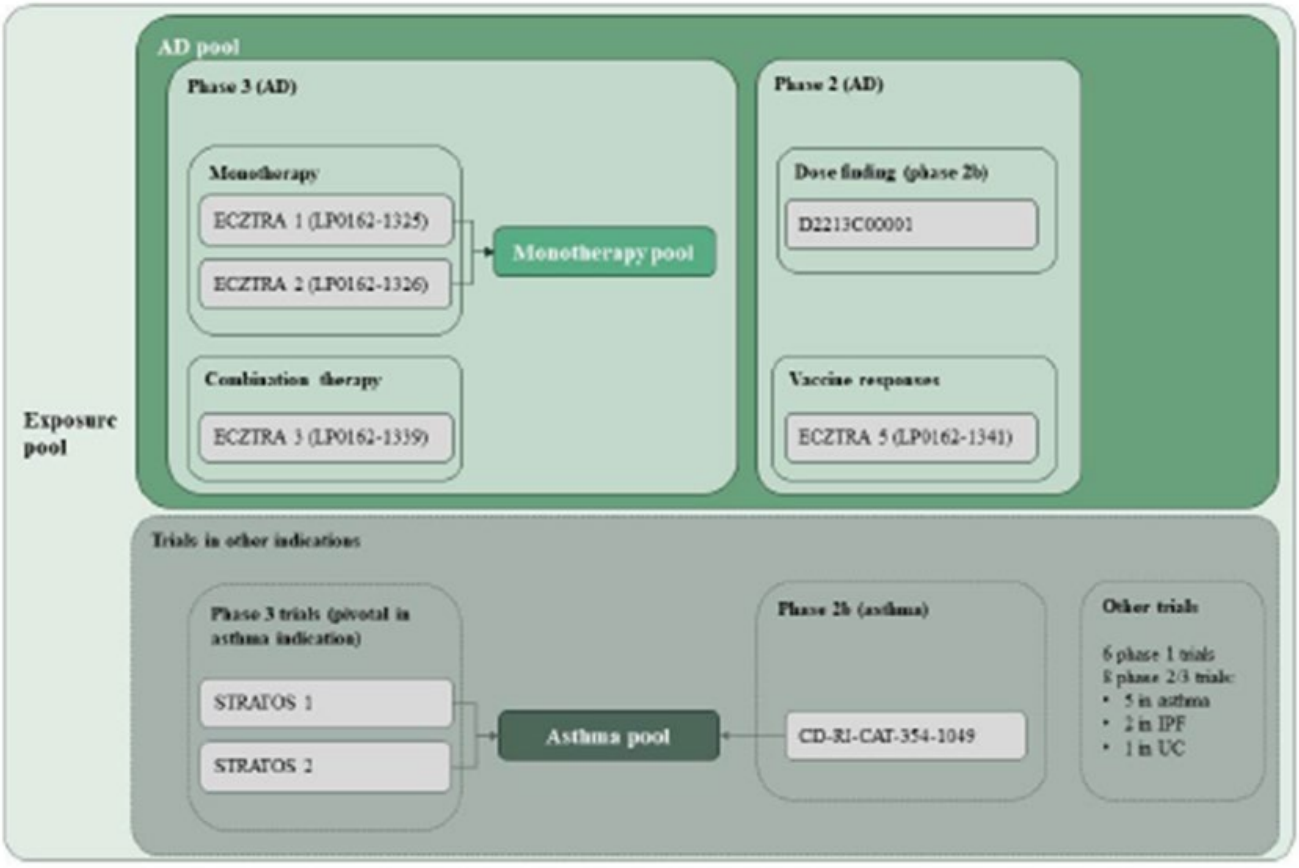

Figure 26 Overview of the safety data pools

Patient exposure

Table 37 shows the number of subjects included in the safety analysis pool.

Table 37 Total exposure in the pools and key trials - entire treatment period

Pool	Tralokinumab		Placebo		Total	
	N	PYE	N	PYE	N	PYE
Exposure pool	4281	3054	2026	1307	5840	4361
AD pool	1991	1404	761	273	2285	1677
Monotherapy pool	1501	1192	477	182	1590	1374
ECZTRA 3	331	168	126	50	378	219
Asthma pool	1528	1395	973	900	2501	2295

Abbreviations: N = total number of subjects; PYE = patient-years of exposure

Notes: AD pool: tralokinumab 300 mg dose exposure only. Exposure pool: all doses of IMP in all AD and non-AD trials. Total N ≠ N (tralokinumab) + N (placebo) in AD pool due to re-randomisation at Week 16 in ECZTRA 1, 2, and 3. Subjects may contribute with exposure to more than one treatment group, the exposure is then presented accordingly. Safety analysis set

Exposure pool

In all completed trials with tralokinumab across all indications (healthy subjects, AD, asthma, UC, and IPF), 4281 subjects received at least one dose of tralokinumab (3054 Patient-Years of Exposure (PYE)) and 2026 subjects received the placebo (1307 PYE).

Patient exposure in AD pool

In the 5 completed AD studies, 1991 subjects were exposed to tralokinumab with a total exposure of 1404 PYE. The exposure to tralokinumab gradually declined over time with the completion of the trials: dose-finding trial (Week 12), ECZTRA 5 (Week 16) and ECZTRA 3 (Week 32), and the re-randomisation of a third of the tralokinumab Week-16 responders to placebo at Week 16 in ECZTRA 1 and 2 (Table 38).

The majority of subjects in the tralokinumab treatment groups were exposed to tralokinumab for ≥16 weeks (AD pool: 90.1%; monotherapy pool: 92.7%; ECZTRA 3 trial: 91.7%).

In total, 807 subjects (821 PYE) were exposed to tralokinumab for ≥52 weeks compared with 31 subjects (31 PYE) exposed to placebo for ≥52 weeks. These subjects were all from the monotherapy pool (ECZTRA 1 and 2).

Table 38 Cumulative exposure by week - AD pool - entire treatment period

	Tralokinumab total		Placebo total	
Duration of exposure	N (%)	PYE	N (%)	PYE
>= 0 weeks	1991 (100.0)	1404	761 (100.0)	272.7
>= 8 weeks	1924 (96.6)	1399	707 (92.9)	268.7
>= 12 weeks	1885 (94.7)	1392	680 (89.4)	264.0
>= 16 weeks	1794 (90.1)	1370	617 (81.1)	248.8
>= 20 weeks	1545 (77.6)	1293	153 (20.1)	105.5
>= 24 weeks	1495 (75.1)	1273	139 (18.3)	99.8
>= 28 weeks	1449 (72.8)	1251	126 (16.6)	93.6
>= 32 weeks	1387 (69.7)	1217	119 (15.6)	89.7
>= 36 weeks	1122 (56.4)	1053	76 (10.0)	63.1
>= 40 weeks	886 (44.5)	888.8	37 (4.9)	36.1
>= 44 weeks	857 (43.0)	866.1	34 (4.5)	33.8
>= 48 weeks	831 (41.7)	844.0	31 (4.1)	31.1
>= 52 weeks	807 (40.5)	821.4	31 (4.1)	31.1

Weeks rounded to next whole number of weeks. Exposure duration during trial is shown by treatment; the same subject may contribute with exposure time in more than one column. All tralokinumab treatment regimens are included.

Exposure end during trial is defined relative to the end-of-treatment visit in the individual trial (W12/W16/W32/W52/W68 if available) or alternatively date of permanent discontinuation of IMP. Safety analysis set.

N = Number of subjects with exposure. PYE = Patient-years of exposure.

In the **monotherapy pool (ECZTRA 1 and 2)**, the exposure to tralokinumab (Q2W and Q4W) during the maintenance treatment period was approximately half that of the tralokinumab exposure during the initial treatment period (172 vs 354 PYE). In contrast, tralokinumab exposure during the open-label period (tralokinumab Q2W with optional use of TCS) was almost twice that obtained during the initial period (665 vs 354 PYE).

The total exposure during the maintenance period was higher in subjects re-randomised to tralokinumab Q2W (85 PYE) and Q4W (88 PYE) than in subjects re-randomised to placebo (38 PYE) and higher than in Week 16 placebo responders maintained on placebo (29 PYE). Approximately half of the subjects entering the maintenance period completed the maintenance period.

In total, 1121 subjects were allocated to the open-label treatment group (tralokinumab Q2W with optional use of TCS) corresponding to a total exposure of 665 PYE and a mean and median exposure of 31 and 36 Patient-Weeks of Exposure (PWE) (Table 39).

Table 39 Summary of exposure time - monotherapy pool - entire treatment period - safety analysis set

	Tralokinumab Q2W (n=1194)		Tralokinumab Q4W (n=165)		Tralokinumab Q2W + optional TCS (open-label) (n=1121)		Tralokinumab total (n=1501)		Placebo (n=477)	
Number of subjects, N	1194		165		1121		1501		477	
PYE (years)	439.2		87.7		664.9		1191.8		181.9	
PWE (weeks)										
Mean (SD)	19.2 (11.0)		27.7 (11.8)		31.0 (11.4)		41.4 (15.3)		19.9 (11.6)	
Median	16.0		35.9		36.0		51.8		16.0	
Q1;Q3	15.9;16.3		16.0;36.1		26.1;36.2		34.4; 52.1		15.8;17.6	
Min;Max	0.04;56.2		2.0;38.1		0.1;53.1		0.04;68.5		0.04;55.1	
Exposure time, N [%]										
N	1194		165		1121		1501		477	
<6 weeks	26	(2.2%)	4	(2.4%)	32	(2.9%)	29	(1.9%)	22	(4.6%)
6 - 11 weeks	37	(3.1%)	23	(13.9%)	68	(6.1%)	50	(3.3%)	30	(6.3%)
12 - 17 weeks	942	(78.9%)	16	(9.7%)	90	(8.0%)	98	(6.5%)	300	(62.9%)
18 - 23 weeks	48	(4.0%)	9	(5.5%)	63	(5.6%)	60	(4.0%)	26	(5.5%)
24 - 29 weeks	13	(1.1%)	7	(4.2%)	60	(5.4%)	72	(4.8%)	15	(3.1%)
30 - 35 weeks	9	(0.8%)	5	(3.0%)	72	(6.4%)	71	(4.7%)	8	(1.7%)
36 - 41 weeks	9	(0.8%)	101	(61.2%)	668	(59.6%)	252	(16.8%)	41	(8.6%)
42 - 47 weeks	9	(0.8%)			4	(0.4%)	38	(2.5%)	4	(0.8%)
48 - 51 weeks	4	(0.3%)			2	(0.2%)	24	(1.6%)		
>=52 weeks	97	(8.1%)			62	(5.5%)	807	(53.8%)	31	(6.5%)

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Abbreviations: N = number of subjects; PWE = patient-weeks of exposure; PYE = patient-years of exposure; Q2W = every 2 weeks; Q4W = every 4 weeks; Q1 = 1st quartile; Q3 = 3rd quartile; SD = standard deviation; TCS = topical corticosteroid

Notes: The tralokinumab Q2W column is the total exposure to tralokinumab Q2W from the initial treatment period plus those re-randomised to tralokinumab Q2W for the maintenance treatment period. Weeks are rounded to next whole number of weeks. Exposure duration by treatment; the same subject may contribute with exposure time in more than one column.

In the **combination therapy (ECZTRA 3)**, 243 subjects were exposed to tralokinumab + TCS and 123 subjects were exposed to placebo + TCS. 226 subjects (92.6%) and 117 (94.4%) completed week 16. N=160 patients (48.3%) were exposed to tralokinumab Q2W +TCS for >30 weeks.

At data lock point 1 (27-Jun-2019), all subjects had completed the treatment periods (Week 32). At this date, 43 subjects were still in the safety follow-up period.

In the **phase 2b dose finding study (D2213C00001)**, 204 subjects were randomised. Tralokinumab was administered as 2 SC injections of 1 mL each, Q2W for 12 weeks for a total of 6 doses. Safety and tolerability were assessed as secondary endpoints. A total of 25 Japanese subjects were randomised.

Patient exposure in asthma pool (supporting data)

In the 3 asthma studies, 1528 subjects received tralokinumab (all dosing frequencies), 973 subjects received placebo. Subjects were treated every 2 weeks (tralokinumab 300 mg Q2W or placebo), and

the total exposure time for subjects exposed to tralokinumab was 1395.2 PYE. A total of 84.4% of the subjects treated with tralokinumab 300 mg Q2W received IMP for at least 52 weeks.

The applicant has provided data from the asthma pool in support of the long-term safety of tralokinumab in the AD indication. This data is considered as supporting data only and limitations in extrapolating fully to the AD population are acknowledged. In terms of exposure to tralokinumab in the asthma pool, the table below highlights that limited numbers of patients were treated with tralokinumab in the longer term up to 52 weeks (between 42-51 weeks: n=38).

Table 40 Exposure time – tralokinumab total and placebo total – asthma pool – safety analysis set

	Tralokinumab 300 mg Total (n=1528)	Placebo Total (n=973)
Exposure time, PYE		
N	1528	973
Sum	1395.2	900.3
Mean (SD)	0.91 (0.231)	0.93 (0.220)
Median	1.00	1.00
Q1;Q3	0.99; 1.00	0.99; 1.00
Min;Max	0.0; 1.1	0.0; 1.1
Duration of exposure (weeks) N (%)		
N	1528	973
0-11	68 (4.5%)	39 (4.0%)
12-21	56 (3.7%)	32 (3.3%)
22-31	34 (2.2%)	17 (1.7%)
32-41	43 (2.8%)	22 (2.3%)
42-51	38 (2.5%)	18 (1.8%)
>=52	1289 (84.4%)	845 (86.8%)

Ongoing trials

In the **ongoing AD extension trial (ECZTEND)**, 1245 subjects have been exposed to tralokinumab. Of the subjects in ECZTEND who came from completed AD trials (ECZTRA 1, 2, 3, and 5) 659 subjects from the ECZTRA 1 and 2 trials, and 260 subjects from ECZTRA 3 trial 630 subjects have been exposed to tralokinumab for a total of ≥18 months and 147 subjects have been exposed to tralokinumab for a total of ≥24 months.

Long-term exposure to tralokinumab (≥12 months) is presented in Table 41. It corresponds to the cumulative exposure to tralokinumab for subjects who started tralokinumab exposure during ECZTRA 1, 2, 3, or 5 combined with their exposure in ECZTEND.

Table 41 Long-term exposure to tralokinumab (≥12 months) - ongoing trial data

Exposure time	Number of subjects exposed
	Tralokinumab N
≥12 months	1209
≥18 months	630
≥24 months	147

Abbreviation: N = number of subjects

Notes: Cumulative long-term exposure to tralokinumab was based on subjects' exposure from completed trials in the AD pool (ECZTRA 1, 2, 3, and 5) combined with their exposure in the long-term extension trial (ECZTEND).

Adverse events

Initial treatment period

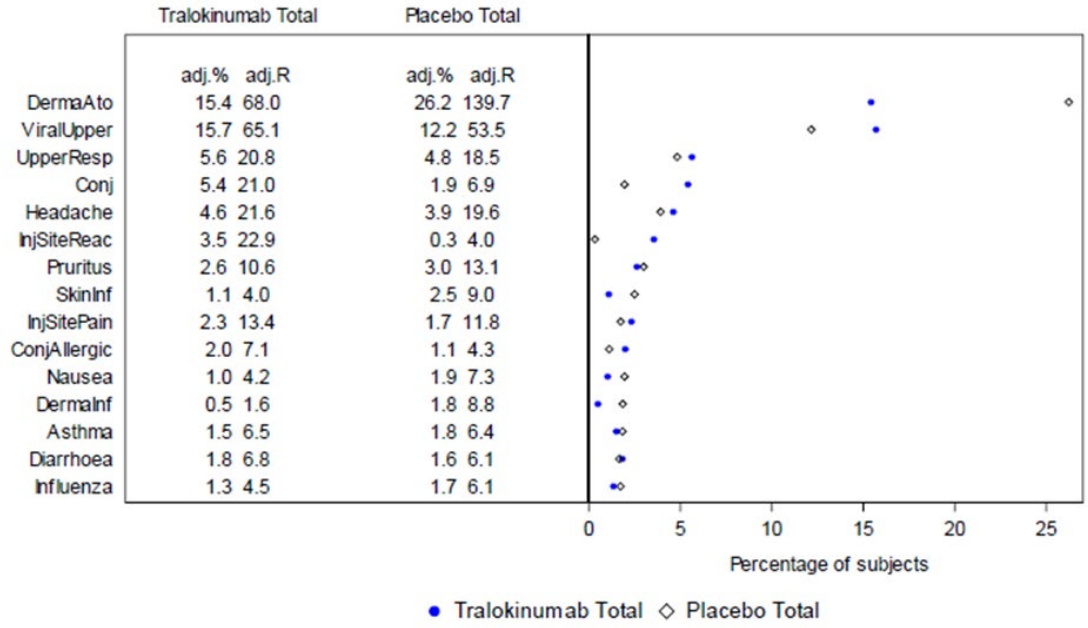
In the initial treatment period of the AD pool, about 66% of patients experienced one or more treatment emergent AEs, in the tralokinumab group as well as in the placebo group (Table 42). Most AEs were mild or moderate, severe AEs occurred in 5% of the tralokinumab group and 6% of the placebo group.

Table 42 Overall summary of AEs - initial treatment period - AD pool - safety analysis set

	Tralokinumab Total (n=1605, PYE=473.19)				Placebo Total (n=680, PYE=193.1)			
	N	(adj.%)	E	adj.R	N	(adj.%)	E	adj.R
Events	1080	(65.7)	3148	639.5	449	(67.2)	1276	678.3
Serious	37	(2.1)	38	7.4	18	(2.8)	22	11.9
Severity								
Mild	881	(53.2)	2127	429.8	326	(49.0)	738	391.0
Moderate	518	(31.5)	917	189.5	258	(39.0)	478	254.3
Severe	77	(4.6)	104	20.2	40	(6.3)	60	33.0
Action taken with IMP								
Drug withdrawn	38	(2.3)	47	9.9	20	(2.8)	25	13.3

AEs collected during the exposure time in the initial treatment period are shown. n: Number of subjects. IMP: Investigational medicinal product. 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 CMH weights. adj. R: Adjusted rate calculated using CMH weights.

The following common AEs occurred more frequently in the tralokinumab group as compared to the placebo group infection (Figure 27): viral upper respiratory tract infection (16% versus 12%) and upper respiratory tract infection (5.6% versus 4.8%); conjunctivitis (5.4% versus 1.9%) and allergic conjunctivitis (2% versus 1.1%); headache (4.6% versus 3.9%); injection site reactions (3.5% versus 0.3%) and injection site pain (2.3% versus 1.7%).



adj. %: Adjusted percentage calculated using CMH weights. adj. R: Adjusted rate calculated using CMH weights. %: Percentage of subjects with one or more events. R: Rate (number of events divided by patient years of exposure multiplied by 100). The 15 most frequent PTs have been selected. In case the subsequent PTs have the same incidence these are included as well. Abbreviations: See List of SOC and PT abbreviations.

Figure 27 Dot plot of most frequent AEs in any treatment group by Preferred Term, in the initial treatment period of the AD pool

In the initial treatment periods of the monotherapy pool and of the combination therapy trial, the pattern and occurrence of AEs was similar as in the AD pool. Of the less frequently occurring AEs in the combination therapy trial, AEs that occurred more frequently in the tralokinumab + TCS group as compared to the placebo + TCS group were: diarrhoea (3.2% versus 1.6%), sinusitis (2.8% versus 0.8%).

Maintenance treatment

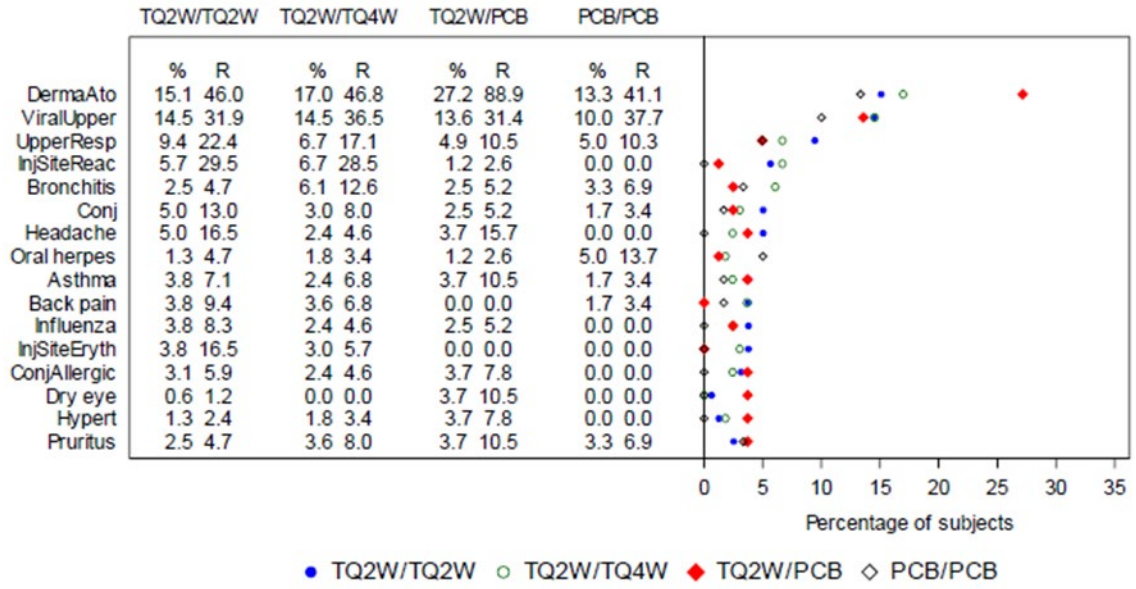
In the maintenance period of the 16-week responders in the monotherapy pool, the proportion of patients with at least one AE was highest in the Q2W group, followed by the placebo group and the Q4W group (Table 43).

Table 43 Summary of Adverse Events in the maintenance treatment period of the monotherapy pool

	Week 16 Tralokinumab responders												Week 16 Placebo responders			
	Tralokinumab Q2W (n=159, PYE=84.73)				Tralokinumab Q4W (n=165, PYE=87.65)				Placebo (n=81, PYE=38.23)				Placebo (n=60, PYE=29.17)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Events	116	(73.0)	423	499.3	109	(66.1)	363	414.2	57	(70.4)	169	442.1	34	(56.7)	88	301.7
Serious	1	(0.6)	1	1.2	6	(3.6)	8	9.1					1	(1.7)	1	3.4
Severity																
Mild	102	(64.2)	280	330.5	94	(57.0)	284	324.0	44	(54.3)	114	298.2	26	(43.3)	56	192.0
Moderate	62	(39.0)	138	162.9	45	(27.3)	74	84.4	27	(33.3)	48	125.6	17	(28.3)	30	102.9
Severe	4	(2.5)	5	5.9	5	(3.0)	5	5.7	3	(3.7)	7	18.3	1	(1.7)	2	6.9
Action taken with IMP																
Drug withdrawn	3	(1.9)	3	3.5	2	(1.2)	2	2.3								

AEs collected during the exposure time in the maintenance treatment period are shown. n: Number of subjects. Q2W: Every 2 weeks. Q4W: Every 4 weeks. IMP: Investigational medicinal product. PYE: Patient-years of exposure. 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).

Common AEs that occurred more frequent in tralokinumab treated groups (Q2W and Q4W versus placebo) were: viral upper respiratory tract infection (15% and 15% versus 14%) and upper respiratory tract infection (9.4% and 6.7% versus 4.9%) and bronchitis (2.5% and 6.1% versus 2.5%), influenza (3.8% and 2.4% versus 2.5%), injection site reactions (5.7% and 6.7% versus 1.2%) and injection site erythema (3.8% and 3.0% versus 0%), conjunctivitis (5.0% and 3.0% versus 2.5%), headache (5.0% and 2.4% versus 3.7%) and back pain (3.8% and 3.6% versus 0%). The higher occurrence of viral upper respiratory tract infections in tralokinumab treated groups was numerically small. The occurrence of allergic conjunctivitis, asthma and pruritis was similar or lower in the tralokinumab treated groups as compared to the placebo group (Figure 28).



%: Percentage of subjects with one or more events. R: Rate (number of events divided by patient years of exposure multiplied by 100). The 15 most frequent AEs have been selected. In case the subsequent AEs have the same incidence these are included as well. Abbreviations: See List of SOC and PT abbreviations.
TQ2W/TQ2W: Week 16 Tralokinumab responder - Tralokinumab every two weeks.
TQ2W/TQ4W: Week 16 Tralokinumab responder - Tralokinumab every four weeks.
TQ2W/PCB: Week 16 Tralokinumab responder - Placebo.
PCB/PCB: Week 16 Placebo responder - Placebo.

Figure 28 Dot plot of most frequent AEs in any treatment group by Preferred Term, in the maintenance treatment period of the monotherapy pool

Comparing tralokinumab Q2W, tralokinumab Q4W, and the group of subjects re-randomised to placebo, there was a tendency towards a dose-response relationship (Q2W > Q4W > placebo) for conjunctivitis, injection site erythema, and upper respiratory tract infection (but not viral upper respiratory tract infection).

The occurrence and pattern of AEs in responders continuing Q2W in the maintenance period (Figure 28) was similar or lower as compared to the initial treatment period (Figure 27).

Asthma pool – supporting data

In the asthma pool, the overall adjusted incidence and rate of AEs during treatment were higher for tralokinumab total vs placebo total (73.2 vs 67.7%; 405.4 vs 383.5 events per 100 PYE).

Common AEs that occurred with a higher frequency in the tralokinumab groups as compared to the placebo group were: bronchitis (7.8% versus 6.7%) and urinary tract infection (4.7% versus 3.8%) and influenza (3.7% versus 2.9%); headache (8.5% versus 6.6%) and arthralgia (3.6% versus 2.6%); injection site erythema (4.5% versus 0.1%) and injection site reaction (4.0% versus 0.3%); hypertension (3.7% versus 2.7%).

Among the AEs that occurred in a similar frequency were: viral upper respiratory tract infection and upper respiratory tract infection, back pain, and injection site pain.

Serious adverse event/deaths/other significant events

Serious adverse events

Based on results in the AD pool, monotherapy pool and ECZTRA 3 trial alone, the overall frequency of SAEs up to 16 weeks of treatment was lower for tralokinumab vs placebo (2.1% vs 2.8%) (with or without TCS). The frequency of SAEs was low in all trials in AD, with only minor between-trial variations.

For the majority of SAEs, the outcome was recovered/resolved for both tralokinumab and placebo. SAEs were most frequently reported within the SOC 'skin and subcutaneous tissue disorders' occurring at similar adjusted incidence and rate for tralokinumab and placebo.

Most SAEs for tralokinumab were events of 'dermatitis atopic' reported within the first 2 months of treatment (5 events in 5 subjects [0.3%] vs 1 event [0.2%] for placebo).

Two SAEs of 'dermatitis exfoliative generalised' occurred in 2 subjects (0.1%) in the tralokinumab group, while 1 event occurred in the placebo group (0.2%).

Deaths

22 deaths occurred in tralokinumab trials in other indications than AD: 12 deaths in asthma [6 for tralokinumab (0.3%; 0.3 deaths per 100 PY) and 6 for placebo (0.5%; 0.4 deaths per 100 PY)] and 10 deaths in IPF [8 for tralokinumab (6.1%; 5.5 deaths per 100 PY) and 2 for placebo (3.3%; 2.9 deaths per 100 PY)].

2 deaths occurred during the AD trials and an additional 3 deaths occurred after trial. The death causes of the 5 subjects with AD who died during or after the trials were described as: unknown/ 'might be cardiac'; septic shock and respiratory failure; pneumonia and septic shock; myocardial infarction; metastatic squamous cell carcinoma.

A 57-year-old male died during the dose-finding trial which was identified as possible 'cardiac event'.

In ECZTRA 5 a 50-year-old female experienced a multitude of AEs and SAEs before eventually dying during the follow-up period of 'failure to thrive', 'encephalopathy', 'acute hepatic failure', 'respiratory failure', 'septic shock' and 'pneumonia'.

In addition, 3 deaths occurred after lock of the clinical database and are therefore only included in the safety database (a 62-year-old male subject 'myocardial infarction', 51-year-old male - 'pneumonia', a 24-year-old female - 'metastatic squamous cell carcinoma').

Other significant events

In the initial treatment period of the AD pool, the adjusted incidence and rate of any severe **infection** and any serious infection were lower for tralokinumab than for placebo. There were 10 subjects (0.6%, 2.1 events per 100 PYE) and 9 subjects (1.4%, 5.8 events per 100 PYE) severe infections, and 6 subjects (0.4%, 1.3 events per 100 PYE) and 7 subjects (1.1%, 3.7 events per 100 PYE)) serious infections in the tralokinumab group versus the placebo group. Similarly, infections requiring medical treatment were less frequent in the tralokinumab group. Opportunistic infections were reported in 56 subjects (3.4 %, 13.0 events per 100 PYE) in the tralokinumab group and in 32 subjects (4.9 %, 21.3 events per 100 PYE) in the placebo group. Endoparasitosis or tuberculous infection did not occur.

In the initial treatment period of the AD pool, the adjusted incidence and rate of **eye disorders (adverse event of special interest [AESI])** were higher in the tralokinumab group than in the placebo group with 7.9% versus 3.4% and 31.1 events per 100 PYE versus 12.9 events per 100 PYE. **Conjunctivitis (AESI)** occurred more frequently in AD patients who received tralokinumab (7.5%, 29.0 event per 100 PYE) compared to placebo (3.2%, 12.3 event per 100 PYE) in the initial treatment period of up to 16 weeks in the pool of 5 studies. Conjunctivitis (as preferred term [PT]) was reported at a higher frequency in patients with severe atopic dermatitis compared to subjects with moderate AD in both the tralokinumab group (6.0 vs 3.3%; initial treatment period) and placebo group (2.2 vs 0.8%; initial treatment period). Most patients recovered or were recovering during the treatment period. Keratitis (as PT) was reported in 0.5% of subjects treated with tralokinumab during the initial treatment period. Of these, half were classified as keratoconjunctivitis, all were non-serious and mild or moderate in severity, and none led to treatment discontinuation.

In the quartile analysis of the ER relationship assessing incidence of conjunctivitis versus exposure in the phase 3 trials, a higher incidence of conjunctivitis was observed in each exposure quartile of subjects receiving tralokinumab than in subjects receiving placebo. However, no relationship between exposure and the incidence of conjunctivitis was observed across quartiles of exposure.

Skin infections requiring systemic treatment (AESI) (2.6% versus 5.5%) and **eczema herpeticum** (AESI) (0.3% versus 1.5%) occurred less in tralokinumab as compared to placebo in the initial treatment period of up to 16 weeks in the pool of 5 studies in AD. Across all treatment periods in the pool of 5 studies, all eczema herpeticum events reported in the tralokinumab group were non-serious, none were severe, and a single event led to permanent discontinuation of treatment.

In the initial treatment period of the AD pool, on tralokinumab there were more patients with clinically relevant increases in the number of **eosinophils** as compared to the placebo group (23.5% versus 9.7%). This difference is also visible in the shift table from baseline to the highest post-baseline value. Most subjects were recovered or were recovering during the trial (see also 'laboratory findings' section).

In the entire treatment period of the AD pool, no events of **anaphylaxis** (reported within 2 days after IMP administration) occurred. In the Asthma pool, there were some occurrences of anaphylaxis (reported within 2 days after IMP administration): 6 events reported by 3 subjects in the tralokinumab

total group and 4 events reported by 2 subjects in the placebo total group. In the tralokinumab total group, the events were all non-serious and had mild or moderate intensity. with similar adjusted incidence and rate for tralokinumab and placebo (0.2% versus 0.2%; 0.38 events per 100 PYE versus 0.44 events per 100 PYE).

Injection site reactions (including pain and redness) occurred more frequently in patients who received tralokinumab (7.2%) compared to placebo (3.0%) in the initial treatment period of up to 16 weeks in the pool of 5 studies. Across all treatment periods in the 5 studies in atopic dermatitis, the vast majority (99%) of injection site reactions were mild or moderate in severity, and few patients (< 1%) discontinued tralokinumab treatment. Most injections site reactions reported had a short duration with approximately 76% of the events resolving within 1 to 5 days.

In the AD pool, comprising 5 clinical trials in AD, a total of 31 **malignancies** (tralokinumab total: 24 events; placebo total: 7 events) were captured by the SMQ (MedDRA) 'Malignant or unspecified tumour' (narrow scope) search over the entire trial period, including all treatment periods (placebo-controlled and open-label) and the safety follow-up period.

The proportion of subjects with events was 0.9% for tralokinumab (total n=1991) and 0.7% for placebo (total n=761). The event rate for tralokinumab was 1.4 per 100 PYO [95% CI: 0.9; 2.1] and for placebo 2.2 per 100 PYO [95% CI: 1.1; 4.6]. Hence, the rate ratio for tralokinumab vs placebo was 0.6 [95% CI: 0.3;1.5].

The majority of the events in both treatment groups were reported within the HLT 'Skin neoplasms malignant and unspecified (excl melanoma)', tralokinumab: 19 of 24 events; placebo: 4 of 7 events; the PTs were 'squamous cell carcinoma of the skin', 'basal cell carcinoma', and 'Bowen's disease'. The remaining events were reported across different organ systems, with no apparent latency in relation to treatment with IMP and no clustering of events over time.

Few of the events were serious or severe, with no notably differences between treatment groups.

A total of 12 **cardiovascular events (CV)** of interest were identified in the AD pool (all doses) during the trial (tralokinumab total: 9 events; placebo total: 3 events). The applicant outlined that considering that the observation time was ~5.5 times higher for tralokinumab than placebo, the incidence and rate of CV events of interest were similar in the tralokinumab total group and the placebo total group (0.4 vs 0.3%). The events had an onset throughout the entire trial durations with no apparent latency or clustering of events over time observed. One event of Ischaemic stroke occurred in the ECZTRA 3 trial. In ongoing trials ECZTRA 6 one of the SAEs ('cerebrovascular accident') in a subject led to permanent discontinuation of IMP. According to an external neurologist who evaluated the case, the stroke was unlikely to be attributable to the IMP, as the subject had several risk factors contributing to the event. 'Transient ischaemic attack' was reported by 4 subjects (5 events) in the tralokinumab total group and with no reports in the placebo group. Three of these 4 subjects had a relevant medical history of transient ischaemic attack, angina pectoris and/or hypertension, and all 3 were also overweight or obese. In addition, 1 subject treated with tralokinumab in ECZTRA 1 died from a myocardial infarction approximately 8 months after the last dose of IMP.

Two events related to **suicidality** were captured across the AD programme, 1 event of overdose and 1 event of depression suicidal. Both events were SAEs and reported in the tralokinumab Q2W group in ECZTRA 2 in the initial treatment period. None of the events were considered related to tralokinumab, and for both events several external stressors were reported as alternative aetiologies.

Laboratory findings

No clinically relevant changes in red blood cells, platelets, or white blood cells were observed, based on the evaluation of mean values, potentially clinically significant values, shifts from baseline, and AEs, with the exception of eosinophils.

Eosinophil levels

AEs of eosinophilia (PTs 'eosinophil count increased' and 'eosinophilia'), were reported by a higher proportion of subjects with tralokinumab than with placebo in the AD pool initial period (Table 44), the monotherapy pool (initial, maintenance and open-label period) and ECZTRA 3 (initial and continuation period). There was no indication of increasing incidences or worsening of severity of AEs of eosinophilia in the maintenance or open-label treatment period of the monotherapy pool compared with that of the initial treatment period. The majority of the subjects reporting AEs of 'eosinophil count increased' and 'eosinophilia' during the AD pool initial period and the monotherapy pool (initial, maintenance and open-label period) had elevated eosinophil levels at baseline (>0.5×109/L).

Table 44 Summary of adverse events related to eosinophilia by PT - initial treatment period - AD pool - adjusted pooling - safety analysis set

	Tralokinumab total (n=1605, PYE = 473.2)				Placebo total (n=680, PYE = 193.1)			
PT	N	(adj.%)	E	adj.R	N	(adj.%)	E	adj.R
Eosinophil count increased	7	(0.5)	7	1.6	0	(0)	0	0
Eosinophilia	15	(0.9)	18	3.9	2	(0.3)	2	1.1

The majority of the events were mild or moderate in severity, and most subjects were recovered/resolved or recovering/resolving from the event in both treatment groups. 1 subject reported 2 severe events (PT 'eosinophilia') in the initial period of which 1 was also an SAE.

Across the complete trials in AD (all trial periods), no events of serious eosinophilic conditions (including eosinophilic granulomatosis with polyangiitis) or drug reactions with eosinophilia and systemic symptoms (DRESS) were reported in subjects treated with tralokinumab.

Liver Function Tests

No subjects in the AD pool reported 'drug-induced liver injury'.

Mean levels of ALP, ALT, AST, BILI, and GGT exhibited minor fluctuations, within the normal ranges, during the initial treatment period of the AD pool (ECZTRA trials only), the maintenance periods of the monotherapy pool and the initial period of the combination therapy trial (ECZTRA 3).

Mean ALP levels increased with tralokinumab from baseline to Week 4 and then gradually declined over the course of the trial. Mean levels for placebo were stable, and tralokinumab and placebo mean ALP levels remained within the normal ranges throughout the trial period.

Hepatobiliary disorders

A number of AEs were reported relating to changes in liver parameter measurements throughout the entire trial period of the AD pool (tralokinumab: 99; placebo: 23).

The adjusted incidence and rate of AEs within the hepatobiliary disorders SOC was low and similar between tralokinumab and placebo during the initial trial period of the AD pool (0.2 vs 0.4%; 0.7 vs 1.6 events per 100 PYE).

An overall higher proportion and rate of hepatobiliary disorders was reported with tralokinumab than placebo when looking across the entire treatment period (1.0 vs 0.4%; 1.5 vs 0.9 events per 100 PYO).

Few hepatobiliary disorder terms were reported by more than 1 subject on tralokinumab or placebo. The most common PTs within this SOC were 'hyperbilirubinaemia' (0.3 vs 0.1%) and 'hepatic steatosis' (0.2 vs 0.1%).

1 SAE of 'acute hepatic failure' was reported with tralokinumab in a subject who experienced a multitude of AEs and SAEs (see' SAE/death section').

Vital signs, physical findings, and other observations related to safety

Vital signs were measured in all trials in AD whereas routine ECG monitoring was only included in the phase 3 ECZTRA trials.

Monoclonal antibodies, like tralokinumab, are not expected to interact directly with ion channels due to the large size and high specificity, thus a thorough QT/QTc trial was not planned. Instead, a blinded external expert conducted evaluations on the ECG data.

No clinically relevant changes in vital signs (diastolic blood pressure, systolic blood pressure, pulse rate) or ECG were observed, based on the evaluation of mean values, potentially clinically significant values, and AEs.

No cardiac safety concerns were observed, based on the centralised ECG evaluation by external cardiovascular ECG experts. No formal QT/QTc study was undertaken during the tralokinumab AD clinical development, the analysis of routine ECGs recorded during the phase 3 ECZTRA trials did not indicate a specific safety concern.

Safety in special populations

Safety in special groups and situations is primarily based on subgroup analysis of AE data.

The AE evaluation related to intrinsic and extrinsic factors focused on incidence rather than event rate, due to the fact that the analysis was based on the 16-week initial treatment period for all subjects.

Elderly (≥ 65 years)

In the AD pool, 109 subjects (4.8%) were elderly (aged ≥65 years), of whom 77 were exposed to tralokinumab. Independent of treatment group, the overall incidence of AEs appeared to be lower in elderly subjects than in younger adult subjects. This difference was mainly driven by lower incidence in elderly subjects for 'dermatitis atopic' and 'viral upper respiratory tract infection'. Except for these 2 types of events, the AE profiles were overall similar between the elderly age group and the younger adult population. Thus, no dose adjustment is recommended for elderly patients.

Renal and hepatic function

For subgroups of renal function (normal function, mildly impaired, and moderately impaired) and for subgroups of hepatic function (normal function and mildly impaired), the incidences of AEs and SAEs were comparable or lower for tralokinumab Q2W vs placebo. Thus, no dose adjustment is recommended in patients with renal or hepatic impairment.

Body Weight

The overall incidence of AEs was comparable between tralokinumab Q2W and placebo for body weight and BMI subgroups, with no clinically relevant differences in the AE profile.

Paediatric population

Safety and efficacy are currently not established for use of tralokinumab in paediatric patients. Data in adolescents is being generated in the ongoing ECZTRA 6 trial. Adolescents are not included in the proposed indication. Additional clinical trials in children (from 6 months of age) are planned as per the paediatric programmes.

Pregnancy and lactation

Tralokinumab has not been studied in pregnant or lactating women, and no information on the excretion of tralokinumab in human milk or effects on the nursing infant is available. The potential risk during pregnancy and lactation is therefore currently unknown (also see 'Non-clinical' section).

In all trials in AD (complete and ongoing) a total of 30 pregnancies in female subjects treated with tralokinumab and 4 pregnancies in partners of male subjects who received tralokinumab were reported (paternal pregnancies were not collected systematically as per protocol in the ECZTRA trials) in the safety database up until 20-Jan-2021. A total of 8 maternal pregnancies were reported in the trials in asthma, of which 5 received tralokinumab (all gave birth to healthy babies). No pregnancies were reported in the trials with tralokinumab in IPF and UC. In all trials with tralokinumab to date, no adverse outcomes have been reported in the babies born by female subjects exposed to tralokinumab. 2 spontaneous abortions in maternal pregnancy cases have been reported: 1 within first week of pregnancy and 1 at gestation-week 4. Of note, 2 maternal pregnancy cases are currently ongoing with final outcome unknown and 2 pregnant female subjects were lost to follow-up without reporting the final outcome to the investigator. 1 adverse outcome has been reported after a paternal pregnancy; the pregnancy outcome was reported as a live baby with congenital anomalies, both of mild severity. Both anomalies had resolved without treatment within 3 months.

Immunological events

Clinical data from the trials with tralokinumab in AD as well as supportive clinical data from other indications (asthma, UC, and IPF) showed that the rate of ADA was low. For the ECZTRA trials, a similar ADA incidence was observed in subjects treated with tralokinumab (1.4%) compared with subjects treated with placebo (1.3%) during the initial 16 weeks of treatment. Furthermore, 2/1553 tralokinumab treated subjects (0.1%) and 1/629 placebo-treated subjects (0.2%) had treatment-emergent NAb during the initial 16 weeks of treatment. Thus, the ADA/NAb incidence after 16 weeks of treatment was low and similar between tralokinumab and placebo confirming the low immunogenicity of tralokinumab. The ADA incidence for subjects who received tralokinumab up to 52 weeks was 4.6%; 0.9% had persistent ADA and 1.0% had neutralising antibodies.

No distinct pattern of AEs was found in the ADA/NAb positive subjects. No immunogenicity related adverse events such as immune complex disease, serum sickness/serum sickness-like reactions, or anaphylaxis were observed with tralokinumab in the AD pool (across all trial periods) and there was no increased risk of serious allergic reactions in the ADA ECZTRA analysis set. Furthermore, there was no indication of an impact of ADA/NAb on PK or efficacy.

See also PK section 'Integrated analysis of immunogenicity'.

Safety related to drug-drug interactions and other interactions

No specific *non-clinical* drug interaction studies were conducted as no drug-drug interactions were expected based on the putative mechanism of tralokinumab. There currently are no clinical data on drug interactions with tralokinumab. A drug-drug interaction (DDI) trial (ECZTRA 4) is ongoing to

determine the DDI potential between tralokinumab and CYP substrates in subjects with AD. With respect to drugs likely to be co-administered with tralokinumab in clinical use, it is expected that combination therapy with TCS will occur in clinical practice. Tralokinumab in combination with TCS was investigated in ECZTRA 3.

See also PK/PD section.

Discontinuation due to adverse events

The most frequent AEs leading to permanent discontinuation of IMP were 'dermatitis atopic' at lower adjusted incidence and rate for tralokinumab vs placebo. The majority of these events had onset within the first 1-2 months of treatment both for tralokinumab (7 events in 7 subjects; onset on Days 12, 14, 15, 23, 38, 60, and 99) and for placebo (10 events in 10 subjects; onset on Days 2, 4, 9, 14, 15, 31, 47, 57, 64, and 69). The AE 'injection site reaction' occurred only in the tralokinumab group with onset within the first 1-3 months (Days 36, 58, 70, 70, and 74). 'Eosinophilia' also only occurred in the tralokinumab group, had onset on Days 22, 43, and 58 (all 3 subjects had elevated eosinophil levels at baseline [range: 0.8-3.3×109/L]). The AE 'conjunctivitis' also only occurred in the tralokinumab group onset on Days 16 and 19. All other AEs leading to permanent discontinuation of IMP were single events for each PT within each treatment group.

In the AD Pool AEs leading to permanent discontinuation of IMP occurred at similar incidence and rate for tralokinumab and placebo (2.3 and 2.8%) in the initial treatment period. An overview of the available data relating to discontinuation with longer term use of tralokinumab in AD patients (i.e. beyond 16 weeks treatment) was not provided.

Post marketing experience

Not applicable.

2.6.1. Discussion on clinical safety

Patient exposure

In total, 1991 subjects with AD were exposed to tralokinumab in the 5 completed studies (ECZTRA 1, 2, 3, 5, and dose finding study D2213C00001). In this AD pool, 90.1% of subjects (N=1794) in the tralokinumab treatment groups were exposed to tralokinumab for ≥16 weeks and 40.5% of subjects (N=807) were exposed to tralokinumab for ≥52 weeks. The exposure to tralokinumab gradually declined over time with the completion of the trials. Much of the safety information up to week 52 is acquired from the majority of patients who were non-responders at Week 16 and thus continued tralokinumab Q2W in the open-label fashion. The relatively high percentage of patients who did not complete treatment in the tralokinumab maintenance period was explained by the trial design, whereby approximately 30% of patients treated with tralokinumab ended up transferring to the open-label treatment group (where additional treatment with TCS could be used). Approximately 80% of patients in the open-label study went on to complete treatment.

As mentioned in the clinical efficacy discussion, two sites were prematurely terminated due to GCP compliance issues. From a safety perspective there was uncertainty in relation to the data for the site based in the US; initially, no AEs were reported until questioned by the applicant. The AEs that eventually were reported from the site had a different AE pattern from those observed at other sites. A post-hoc sensitivity analysis excluding the 12 subjects from the statistical analysis concludes no impact on trial conclusion on the confirmatory primary and key secondary endpoints at Week 16.

The size of the safety database and degree of patient exposure for tralokinumab to support this application is overall considered sufficient. The numbers of patients with long term exposure to tralokinumab are somewhat low. Further safety information will be collected in the ongoing long-term safety study (ECZTEND) listed as category 3 in the RMP. The interim and final study reports will be submitted for assessment by Q4 2022 and Q1 2025, respectively.

Adverse events, severe adverse events and death

During the initial treatment period in the AD pool, the proportion of patients who experienced one or more treatment emergent AE during the 16-week treatment period was similar between the patients treated with tralokinumab and placebo (around 66%). Most AEs were mild or moderate, severe AEs occurred in 5% of the tralokinumab group and 6% of the placebo group. The proportion of patients who discontinued treatment due to AEs was low (2.3% in the tralokinumab group and 2.8% in the placebo group).

A similar trend in terms of frequency and severity of AEs was observed in the safety follow-up. The overall incidence and rate of AEs were low and generally similar for tralokinumab and placebo (14.2 vs 12.8%), with the majority of AEs recorded as being mild or moderate in severity. Discontinuation of tralokinumab due to AEs during both the maintenance and open-label treatment was comparatively low 1.5% and 3.1%.

Overall, the most common adverse reactions occurring in ≥ 2% of patients treated with tralokinumab with or without TCS were upper respiratory tract infections (23.4%; mainly reported as common cold), ISR (7.2%), conjunctivitis (5.4%) and conjunctivitis allergic (2.0%).

The frequency of SAEs was low in all trials in AD and for the majority the outcome was recovered/resolved for both tralokinumab and placebo. Most SAEs in patients treated with tralokinumab were events of 'dermatitis atopic' reported within the first 2 months of treatment (5 events in 5 subjects [0.3%] vs 1 event [0.2%] for placebo) which was an expected AE in the treated population. This was also the most frequent AE- leading to permanent discontinuation of the IMP.

On the basis of the available data, there is no evidence that treatment with tralokinumab in AD is associated with an increased risk of death compared with placebo.

Results on common AEs, AE severity, and investigator causality in the supporting data arising from the asthma pool during 52 weeks of treatment with tralokinumab vs placebo were generally in accordance with the results in AD, taking into consideration the differences in aetiology and disease characteristics between the AD and asthma trial populations. The higher frequencies of 'viral upper respiratory tract infection', 'upper respiratory tract infection', and 'conjunctivitis' for tralokinumab vs placebo seen in AD were, however, not observed in the asthma pool. Conjunctivitis rate difference raises the question of ocular or immune difference between AD and Asthma. Whilst the asthma pool is considered as supportive data, it is noted that differences in trial populations occur between both subgroups AD versus asthma patients.

Safety areas of interest

Infections and infestations occurred at similar adjusted incidence and rate for tralokinumab and placebo and any serious infection were lower for tralokinumab than for placebo.

The incidence of 'viral upper respiratory tract infection' during the initial treatment period in the AD pool was higher for tralokinumab (15.7%) than for placebo (12.2%). 'Upper respiratory tract infections' has been listed as an ADR in section 4.8 of the SmPC with a frequency very common.

Skin infections requiring systemic treatment (2.5% versus 5.5%) and eczema herpeticum (0.3% versus 1.5%) occurred less in tralokinumab as compared to placebo in the initial treatment period of

up to 16 weeks. Eczema herpeticum has been described as a selected adverse reaction in section 4.8 of the SmPC.

Across the clinical trials in AD, the frequency of opportunistic infections was lower with tralokinumab treatment compared with placebo. However, some imbalances were observed between the clinical studies in the AD population.

In the continuation treatment period (ECZTRA 3), the rate of opportunistic infections for tralokinumab + TCS total was notably higher than the rate observed for tralokinumab Q2W + TCS in the initial treatment period (28.4 vs 17.3 events per 100 PYE). This increase was not seen during the maintenance treatment period and the open-label arm in the monotherapy pool.

In the AD safety follow up period, the rate of serious infections in the tralokinumab group was slightly higher during follow-up than during treatment (2.4 events per 100 PYFU vs 1.3 events per 100 PYE) but lower than in the placebo group during treatment (3.7 events per 100 PYE).

Similarly, the rates of severe infection requiring antibiotic treatment with tralokinumab Q2W in the maintenance treatment period of the monotherapy pool (4.7 events per 100 PYE) and the open-label arm (5.1 events per 100 PYE) were comparable with tralokinumab Q2W in the initial treatment period 3.4 events per 100 PYE) with a trend towards a numerically higher frequency of these cases over longer term treatment with tralokinumab. It is therefore recommended that this topic continues to be closely monitored as further longer-term data becomes available from routine pharmacovigilance activities.

Eye disorders occurred more frequently in the tralokinumab group (7.9%) than placebo (3.4%) in the initial treatment period of the AD pool. None of the eye disorder were serious and the majority of the events were mild or moderate in severity and responded to treatment with topical preparations.

Epidemiological data have shown that patients with AD have an increased risk of ocular comorbidities, such as conjunctivitis, keratitis, and keratoconus compared with the general population, and the incidence of ocular complications increases with AD severity. The mechanisms underlying this observation are however unclear.

Furthermore, conjunctivitis and conjunctivitis allergic were more frequently reported for tralokinumab vs placebo during the initial treatment period in the AD pool ('conjunctivitis': 5.4 vs 1.9%; 'conjunctivitis allergic': 2.0 vs 1.1%). Subjects with conjunctivitis appeared to have more severe AD at baseline than subjects without conjunctivitis. More than half of the subjects reporting conjunctivitis in the initial treatment period had a history of allergic conjunctivitis or keratoconjunctivitis. Most patients recovered or were recovering during the treatment period. A large variation in the duration of the conjunctivitis events was observed in both treatment groups approximately 25% had a duration of 91 days or longer.

Keratitis was reported in 0.5% of subjects treated with tralokinumab during the initial treatment period. Of these, half were classified as keratoconjunctivitis, all were non-serious and mild or moderate in severity, and none led to treatment discontinuation.

The event rates for 'conjunctivitis', 'conjunctivitis allergic', and 'keratitis' were lower during the continued treatment (16 – 32 weeks) with tralokinumab compared to the initial treatment period. However, among the Week 16 tralokinumab responders, pre-defined eye disorder was reported with a higher incidence and rate in the tralokinumab Q2W + TCS group than in the tralokinumab Q4W + TCS group (4.3 vs 1.4%).

Overall, the rate of conjunctivitis with tralokinumab Q2W in the maintenance treatment period of the monotherapy pool was lower than the rate observed in the initial treatment period with a tendency towards a dose-response in the rate of conjunctivitis reported for tralokinumab Q2W vs Q4W. The

pattern of conjunctivitis events as well as the types of events reported also appeared similar to what was observed in the initial period.

Conjunctivitis has been listed as an ADR in section 4.8 of the SmPC with a frequency common and a statement about conjunctivitis and keratitis has also been added in section 4.4 of the SmPC. Patients treated with tralokinumab who develop conjunctivitis that does not resolve following standard treatment should undergo ophthalmological examination. This ADR will also be monitored and assessed in the ongoing long-term PASS (ECZTEND). Conjunctivitis is also listed as an important potential risk in the RMP.

Injection site reactions (ISRs) were reported more frequently for patients treated with tralokinumab (7.2%) than for placebo (3.0%) in the initial treatment period of up to 16 weeks in the AD pool. A dose dependent effect was also seen, with higher rates of ISRs in the tralokinumab Q2W vs Q4W treated patients. The vast majority (99%) of ISRs were mild or moderate in severity, and few patients (< 1%) discontinued tralokinumab treatment. Most injections site reactions reported had a short duration with approximately 76% of the events resolving within 1 to 5 days.

ISR has been listed in section 4.8 of the SmPC with a frequency common and is further described in the list of selected adverse reactions. In addition, all events related to ISRs, reported from ongoing and future clinical trials and future post-marketing use, will be monitored via routine pharmacovigilance activities.

Eosinophilia was reported at a higher rate in patients treated with tralokinumab (1.3%) compared to placebo (0.3%) during the initial treatment period of up to 16 weeks in the AD pool. However, the incidence was overall low. Tralokinumab-treated patients had a greater mean initial increase from baseline in eosinophil count compared to patients treated with placebo. However, the increase in the tralokinumab-treated patients was transient, and mean eosinophil counts returned to baseline during continued treatment. The safety profile for subjects with eosinophilia was comparable to the safety profile for all subjects. Eosinophilia has been listed in section 4.8 of the SmPC with a frequency common and is further described in the list of selected adverse reactions.

Immunogenicity with tralokinumab was observed in the studies however the incidence was considered low. Across all trial periods, the ADA incidence for subjects who received tralokinumab was 4.6%; 0.9% had persistent ADA and 1.0% had NAb. ADA and NAb responses were not associated with any impact on safety. AEs related to immunogenicity will be followed up via routine pharmacovigilance activities. Immunogenicity has also been described in the list of selected adverse reactions in section 4.8 of the SmPC.

Malignancies were recorded in 31 patients in the AD pool including in all treatment periods (tralokinumab total: 24 events; placebo total: 7 events). The use of immunosuppressant medications has been hypothesised as a potential risk for the development of malignancies. Some uncertainty remains in relation to the potential role of IL-13 in contributing to the development of malignancy and there are conflicting reports in the literature regarding its tumorigenic potential.

Based on the available data, there is no specific safety signal in relation to the occurrence of malignancy with the use of tralokinumab. Nevertheless, the risk of developing malignancy following treatment with tralokinumab in AD patients cannot be completed excluded and long-term data should be provided to adequately characterise this risk through routine pharmacovigilance activities, PSURs and the ongoing long-term ongoing PASS (ECZTEND). Malignancy has also been included as an important potential risk in the RMP.

Headache and migraine occurred more frequently in tralokinumab treated patients as compared to placebo (headache: 8.5% tralokinumab versus 6.3% placebo; migraine: 0.5% tralokinumab vs 0.2% placebo). Following further clarification from the applicant on this issue, it is not recommended at this

time to include these events in the SmPC but they should be monitored through routine pharmacovigilance activities.

Cardiovascular events were included as a safety area of interest. A total of 12 CV events of interest were identified in the AD pool (all doses) during the trial (tralokinumab total: 9 events; placebo total: 3 events). The Applicant's external CV expert outlined that the review of relevant serious CV cases concluded that there was no causal relationship between tralokinumab in 7 out of the 9 SAEs reported. 1 SAE could theoretically be related to the IMP and 1 SAE was most likely not related to the IMP, but a final conclusion for these 2 SAEs could not be made from the available information. Although confounding factors were noted in many CVS cases reported with tralokinumab in the exposure pool, the potential for an association between the cases of CVA/TIA/CV events and thrombosis and possible coagulopathy relating to active treatment with tralokinumab should be monitored. This topic is currently considered as a topic of interest and should continue to be followed in the longer term through the ongoing PASS (ECZTEND).

Suicidality: AD is associated with numerous psychiatric comorbidities, including depression and anxiety. 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. Two events related to suicidality were reported in the tralokinumab Q2W group in ECZTRA 2 in the initial treatment period. None of the events were considered related to tralokinumab. This topic should continue to be routinely monitored and presented for discussion in PSURs as a topic of interest.

Allergy, hypersensitivity and anaphylaxis: No cases of anaphylaxis, immune complex disease, serum sickness, or serum sickness like reactions arising from the use of tralokinumab occurred in the trials in AD. The frequency of serious allergic reactions was low and similar with tralokinumab and placebo.

Pregnancy and lactation

There is limited amount of data from the use of tralokinumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of tralokinumab during pregnancy (section 4.6 of SmPC). Use in pregnant and lactating women has been added as a missing information in the list of safety concerns in the RMP. The safety of tralokinumab use in pregnant women will be monitored in an observational PASS listed as category 3 in the RMP. Annual updates followed by interim and final study report will be submitted for review by Q4 2024 and Q2 2030, respectively.

Dose-effect relationship

A dose response effect was observed with more frequent dosing. This was driven by increases in upper respiratory tract infections and injection site related PTs with the more frequent tralokinumab Q2W dosing regimen vs the Q4W dosing regimen. There was also a consistent increase across trials in the incidence of eye disorders, primarily classified as 'conjunctivitis', with the more frequent dosing regimen Q2W vs the Q4W dosing regimen. ADAs were noted to be higher with tralokinumab 300mg Q4W in the maintenance period.

In the maintenance treatment phase, the occurrence and pattern of common AEs in patients treated with tralokinumab Q2W was basically similar to Q2W in the initial treatment period, while AEs were less frequent in patients treated Q4W.

2.6.2. Conclusions on the clinical safety

The safety profile of tralokinumab has been well characterised in the conducted clinical trials and is

considered acceptable by CHMP. Some safety follow-ups are however requested as mentioned in the safety discussion. Further long-term safety data will also be provided and assessed from the ongoing long-term extension PASS (ECZTEND) and observational safety study in pregnancy listed as category 3 studies in the RMP.

2.7. Risk Management Plan

Safety concerns

Important identified risks	None
Important potential risks	Conjunctivitis Malignancy
Missing information	Use in pregnant and lactating women Long-term safety

In addition, the following topics should continue to be monitored and analysed as adverse events of special interest through routine pharmacovigilance activities and presented in the PSURs. Besides, further longer-term follow-up data should be provided in the long-term extension trial ECZTEND (long-term PASS) of tralokinumab in subjects previously participating in the ECZTRA trials in relation to these adverse events of special interest.

- Systemic hypersensitivity including events associated with immunogenicity
- Effect of conjunctivitis over the longer term
- MACE
- Malignancy with longer term use
- Serious infections
- Suicidal ideation/suicide/depression
- Monitoring for potential tralokinumab-induced arthropathy/enthesitis/tendinopathy
- Safety in patients >65yrs
- Safety in Black or African American patients
- Nature and frequency of ISRs

Pharmacovigilance plan

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3 – Required additional pharmacovigilance activities				
Observational PASS of tralokinumab use in pregnancy. Post-authorisation safety study of tralokinumab use in pregnancy: An observational study based on electronic health care data Planned	To investigate whether maternal exposure to tralokinumab in pregnancy is associated with an increased risk of major congenital malformations, preterm births, infants born small for gestational age, spontaneous abortion, or stillbirths.	- Use in pregnant and lactating women	Annual update (progress reports on number of exposed pregnancies) starting 1 year after launch.	Yearly
			Interim report including feasibility assessment	Q4 2024
			Final report	Q2 2030
PASS investigating long-term safety with tralokinumab. A phase 3 open-label, single-arm, multi-centre, long-term extension trial to evaluate the safety and efficacy of tralokinumab in subjects with atopic dermatitis who participated in previous tralokinumab clinical trials – ECZTEND. Ongoing	The primary objective is to evaluate the long-term safety of tralokinumab. The secondary objective is to evaluate the efficacy of tralokinumab given as continuous treatment, re-treatment, or introduced for the first time in tralokinumab-naïve subjects.	- Long-term safety - Conjunctivitis - Malignancy	Interim clinical trial report	Q4 2022
			Final clinical trial report	Q1 2025

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Conjunctivitis	Routine risk minimisation measures: Communicate to physicians and patients that conjunctivitis is common adverse reaction, and that patients treated with tralokinumab who develop conjunctivitis that does not resolve following standard treatment should undergo ophthalmological examination. Relevant text is provided in the following sections of the SmPC: • Section 4.4 (Special warnings and precautions for use) • Section 4.8 (Undesirable effects) Relevant text is provided in the following sections of the PIL: • Section 2 (What you need to know before you use tralokinumab) • Section 4 (Possible side effects) Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: PASS investigating long-term safety with tralokinumab. A phase 3 open-label, single-arm, multi-centre, long-term extension trial to evaluate the safety and efficacy of tralokinumab in subjects with atopic dermatitis who participated in previous tralokinumab clinical trials – ECZTEND.
Malignancy	No risk minimisation measures are required for patients receiving tralokinumab; standard care is adequate.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: PASS investigating long-term safety with tralokinumab. A phase 3 open-label, single-arm, multi-centre, long-term extension trial to evaluate the safety and efficacy of tralokinumab in subjects with atopic dermatitis who participated in previous tralokinumab clinical trials – ECZTEND.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Use in pregnant and lactating women	Routine risk minimisation measures: Communicate to physicians and patients that there is a limited amount of data from the use of tralokinumab in pregnant women; therefore, as a precautionary measure, it is preferable to avoid the use of tralokinumab during pregnancy. Communicate to physicians and patients that it is unknown whether tralokinumab is excreted in human milk or absorbed systemically after ingestion, so a decision must be made whether to discontinue breast-feeding or to discontinue tralokinumab therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. Relevant text is provided in the following section of the SmPC: • Section 4.6 (Fertility, pregnancy and lactation) Relevant text is provided in the following section of the PIL: • Section 2 (What you need to know before you use tralokinumab) Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Supplementary surveillance of pregnancy outcomes reported in the post-marketing setting. Additional pharmacovigilance activities: Observational PASS of tralokinumab use in pregnancy. Post-authorisation safety study of tralokinumab use in pregnancy: An observational study based on electronic health care data.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Long-term safety	Routine risk minimisation measures: Communicate to physicians and patients that the long-term safety of tralokinumab was assessed in the 2 monotherapy studies up to 52 weeks and in 1 combination study with TCS up to 32 weeks. The safety profile of tralokinumab through week 52 and week 32 respectively was consistent with the safety profile observed up to week 16. Relevant text is provided in the following section of the SmPC: Section 4.8 (Undesirable effects) – text below the list of adverse reactions Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: PASS investigating long-term safety with tralokinumab. A phase 3 open-label, single-arm, multi-centre, long-term extension trial to evaluate the safety and efficacy of tralokinumab in subjects with atopic dermatitis who participated in previous tralokinumab clinical trials – ECZTEND.

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.4 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant declared that tralokinumab has not been previously authorised in a medicinal product in the European Union.

The CHMP, based on the available data, considers tralokinumab to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Adtralza (tralokinumab) is included in the additional monitoring list as it contains a new active substance.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Tralokinumab is intended for the treatment of moderate-to-severe AD in adult patients who are candidate for systemic therapy.

AD is a chronic or chronically relapsing inflammatory skin disease. It is characterised by eczematous lesions (including erythema, excoriations, lichenification, infiltration, oozing), xerosis and pruritus. These clinical manifestations lead to significant sleep disturbances, severe psychological and sociological sequelae and impaired quality of life especially in patients with moderate-to-severe AD.

The main goals of the treatment are the reduction of inflammation and symptoms, especially of pruritus.

3.1.2. Available therapies and unmet medical need

Patients with mild disease are generally managed with emollients and mild- to moderate-potency TCS.

TCI are considered as an alternative or adjunct treatment to TCS, especially when treatment with TCS is either inadvisable or not possible and when steroid-sparing treatment is needed in sensitive areas, such as face and skin folds. However, patients with moderate-to-severe AD require additional therapies to control skin inflammation and symptoms. These additional therapies include phototherapy, high-potency TCS and, eventually, when topical options fail to control the disease, systemic treatments.

Currently, 2 systemic therapies are centrally approved for patients with AD: dupilumab (Dupixent), an injectable monoclonal antibody against IL4/IL13 approved in 2017 for moderate-to-severe AD in adults and adolescents 12 years and older who are candidates for systemic therapy; baricitinib (Olumiant), a JAK-inhibitor approved in July 2020 for moderate-to-severe AD in adult patients who are candidates for systemic therapy. In addition, two topical treatments (ointments) are approved in AD in the EU: crisaborole (Staquis) a PDE-4 inhibitor and tracrolimus monohydrate (Protopic) a calcineurin inhibitor.

Other therapies are not centrally authorised but are approved in individual member states and recommended by AD treatment guidelines: Oral glucocorticosteroids are intended for severe AD; PUVA is intended for severe AD.

In addition to approved therapies, current AD guidelines and expert advice recommend off-label use of other oral therapies, such as, e.g. methotrexate, azathioprine, and mycophenolate mofetil.

For patients with moderate to severe AD for whom treatment with TCS and or TCIs and/or systemic therapies is insufficient, treatment options are limited, and therefore there is a need for new treatment options.

3.1.3. Main clinical studies

The clinical development programme supporting tralokinumab for the treatment of moderate to severe AD in adults who are candidates for systemic therapy, with or without TCS, is primarily based on 3 adequate and well-controlled pivotal trials:

- Two almost identical tralokinumab phase 3 monotherapy trials (ECZTRA 1 and 2) of 52-week duration where superiority to placebo at Week 16 was tested;
- One phase 3 combination therapy trial (ECZTRA 3) of 32-week duration where superiority of tralokinumab+TCS versus placebo+TCS at Week 16 was tested.

Additionally, the following trials in AD support the efficacy in adults:

- One phase 2 vaccine response trial (ECZTRA 5) evaluating the effect of tralokinumab versus placebo on vaccine antibody responses.

One phase 2b dose-finding trial evaluating the efficacy of 45 mg, 150 mg, and 300 mg tralokinumab in combination with TCS versus placebo+TCS (dose-finding trial; D2213C00001).

3.2. Favourable effects

In the monotherapy (ECZTRA 1 and 2) and combination with TCSs (ECZTRA 3) studies, a significant greater proportion of patients treated with tralokinumab achieved the primary endpoints IGA 0 or 1 and EASI-75 compared to placebo at Week 16.

The proportion of patients with IGA 0 or 1 at Week 16 was 15.8% (ECZTRA 1), 22.2% (ECZTRA 2), 38.9% (ECZTRA 3) in the tralokinumab Q2W groups as compared to 7.1% (ECZTRA 1), 10.9% (ECZTRA 2), 26.2% (ECZTRA 3) in the placebo groups.

The proportion of patients with EASI-75 at Week 16 was 25.0 % (ECZTRA 1), 33.2 % (ECZTRA 2), 56.0% (ECZTRA 3) in the tralokinumab Q2W groups as compared to 12.7% (ECZTRA 1), 11.4% (ECZTRA 2), 35.7% (ECZTRA 3) in the placebo groups.

The key secondary endpoints results for the initial treatment period (change in, reduction of Worst Daily Pruritus NRS (weekly average) ≥4 and change in DLQI score from baseline to Week 16) supported the effects seen in the primary endpoints as statistically significantly better results were reported in patients receiving tralokinumab as compared to patients on placebo. For the vast majority of these endpoints consistent results were reported for the primary, secondary and tertiary estimands and all sensitivity analyses.

Response rates (IGA 0/1 or EASI-75) at Week 52 in the monotherapy pool were 56.2% and 50% for tralokinumab 300 mg Q2W and tralokinumab 300 mg Q4W among subjects achieving clinical response at week 16, respectively. High maintenance of clinical efficacy at Week 32 were seen in the combination therapy study across tralokinumab 300 mg Q2W + TCS and tralokinumab 300 mg Q4W + TCS among subjects achieving clinical response at week 16.

In both monotherapy studies (ECZTRA 1 and ECZTRA 2) and in the concomitant TCS study (ECZTRA 3) tralokinumab improved patient-reported symptoms of AD, as measured by POEM, and the impact of AD on sleep, as measured by Eczema-related sleep NRS, at week 16 compared to placebo. A higher proportion of patients treated with tralokinumab had clinically meaningful reductions in POEM, (defined as at least 4 point improvement) from baseline to Week 16 compared to placebo. These endpoints were not included in the confirmatory testing strategy.

3.3. Uncertainties and limitations about favourable effects

Albeit statistically significant, the effect size in the monotherapy trials was considered small. The clinical relevance and clinical significance of the treatment effect of tralokinumab both as monotherapy and in combination with TCS was therefore questioned during the evaluation.

Subgroup analyses of IGA 0/1 and EASI75 in the monotherapy pool, did not identify any baseline characteristics or selection criteria that were predictive of achieving either of these outcomes at Week 16. Similarly, a post-hoc subgroup analysis of EASI50 did not identify any baseline characteristics or selection criteria that were predictive of achieving a clinically relevant reduction in EASI score at Week 16.

The applicant indicated that IGA 0/1 and EASI-75 are chosen as preferred primary outcomes in clinical trials, however they have outcomes with a lower threshold and that secondary endpoints (such as IGA 0/1/2 and EASI50) are considered more informative for the evaluation of the clinically relevant effects. In the clinical studies, the effect size was indeed increased with lower thresholds which are considered relevant for clinical practice. However, CHMP considered that the increase in efficacy even after consideration of MCIDs instead of primary and secondary outcomes is still modest. Nevertheless, this treatment effect still can be considered as clinically relevant in patients who have not responded to other treatment options. Therefore, the benefit of tralokinumab used as monotherapy, or in combination with TCS is considered to be demonstrated. As better efficacy results were reported in the TCS combination trial (ECZTRA 3) as compared to monotherapy studies the following statement has been included in sections 4.2 the SmPC: "The use of topical corticosteroids, when appropriate, may provide an additional effect to the overall efficacy of tralokinumab".

In ECZTRA 1 and 2 studies, the Q4W dose regimen was found to be less efficacious as compared to the Q2W regimen. For the Q4W dose regimen, a statistically (nominally) significant difference was only reported for the EASI-75 at Week 52 endpoint in the ECZTRA 2 study (within endpoints under multiplicity adjustment). Lower efficacy as compared to the Q2W regimen was also observed for the vast majority of other endpoints investigated in these studies.

Based on the results on IGA0/1 and EASI-75 in the monotherapy pool, efficacy of maintenance treatment with tralokinumab in the Q4W dosing regimen can be accepted, however it is reflected in section 4.2 of the SmPC that Q4W may be less effective than Q2W. It is at the prescriber's discretion, to recommend every fourth week dosing for patients who achieve clear or almost clear skin after 16 weeks of treatment.

In addition, for some subpopulation of patients tapering the dose to every fourth week is not appropriate. The reduced exposure in patients with a high body weight, coupled with the reduced exposure with the Q4W regimen, suggests that the Q4W regimen may not be appropriate for patients with a high body weight. Therefore, the section 4.4 of the SmPC states that for patients with high body weight, who achieve clear or almost clear skin after 16 weeks of treatment, reducing the dosage to every fourth week might not be appropriate.

3.4. Unfavourable effects

Conjunctivitis occurred more frequently in AD patients who received tralokinumab (5.4%) compared to placebo (1.9%) in the initial treatment period of up to 16 weeks in the pool of 5 studies. Conjunctivitis was reported at a higher frequency in patients with severe AD compared to subjects with moderate AD in both the tralokinumab group (6.0 vs 3.3%; initial treatment period) and placebo group (2.2 vs 0.8%; initial treatment period). Most patients recovered or were recovering during the treatment period. Conjunctivitis has been added as ADR with a frequency common in the product information. It is also stated in the SmPC that patients treated with tralokinumab who develop conjunctivitis that does not resolve following standard treatment should undergo ophthalmological examination. In addition, conjunctivitis is considered an important potential risk in the RMP and will be further monitored in the ongoing PASS (ECZTEND) which will investigate long-term safety of tralokinumab.

ISR (including pain and redness) occurred more frequently in patients who received tralokinumab (7.2%) compared to placebo (3.0%) in the initial treatment period of up to 16 weeks in the pool of 5 studies. Most ISR reported had a short duration with approximately 76% of the events resolving within 1 to 5 days. ISR has been listed an ADR with common frequency in the product information and is further described in the list of selected adverse reactions.

Adverse reactions of eosinophilia were reported in 1.3% of patients treated with tralokinumab and 0.3% of patients treated with placebo during the initial treatment period of up to 16 weeks in the pool of 5 studies. Tralokinumab-treated patients had a greater mean initial increase from baseline in eosinophil count compared to patients treated with placebo. However, the increase in the tralokinumab-treated patients was transient, and mean eosinophil counts returned to baseline during continued treatment. The safety profile for subjects with eosinophilia was comparable to the safety profile for all subjects. Eosinophilia has been added as an ADR with a frequency common in the product information and is further described in the list of selected adverse reactions.

Eczema herpeticum was reported in 0.3% of the subjects treated with tralokinumab and in 1.5% of subjects in the placebo group, in the initial treatment period of up to 16 weeks in the pool of 5 studies in AD. Across all treatment periods in the pool of 5 studies, all eczema herpeticum events reported in the tralokinumab group were non-serious, none were severe, and a single event led to permanent discontinuation of treatment. Eczema herpeticum is further described in the list of selected adverse reactions in the product information.

A low immunogenic potential of tralokinumab has been demonstrated in the completed clinical trials, and no impact on the clinical benefit/risk profile was identified. The applicant will continue to monitor this topic through the PASS and ongoing monitoring via routine pharmacovigilance.

A small number of cases of malignancy were reported during the AD clinical trials but causality could not be elucidated. No specific measures are required for patients receiving tralokinumab; standard of care is considered adequate. However, as for other immunomodulatory biologics, malignancy is listed as an important potential risk in the RMP and will be further characterised in the ongoing PASS (ECZTEND).

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

3.5. Uncertainties and limitations about unfavourable effects

Uncertainties remain in relation to the overall impact of tralokinumab on the severity and duration of conjunctivitis and the potential impact on patient compliance with longer term use of tralokinumab in AD. As discussed in the previous section, conjunctivitis has been included in the RMP and has been listed as an ADR in the SmPC with a warning, but further characterisation of eye disorders is also required, especially with longer term use of tralokinumab. The effect of conjunctivitis over the longer term will be followed-up through routine pharmacovigilance activities and the ongoing PASS (ECZTEND).

The long-term safety profile of tralokinumab has not been fully characterised due to some limitations in exposure in the AD population and due to the absence of longer term safety data in AD patients. The extension trial (ECZTEND) will provide further long-term data with up to 5 years treatment with tralokinumab (making the total exposure for tralokinumab up to 6 years including the up to one-year treatment in the parent trial). Long-term safety is listed as a missing information in the safety concerns in the RMP.

Overall there were no clear signs of an increased risk for developing malignancies based on results of the AD clinical trials. However, on the basis of the finding of a slight imbalance of cases of malignancy in the treatment group in the AD clinical development programme (tralokinumab total: 24 events; placebo total: 7 events), including case with fatal outcome in a young female patient (fatal metastatic SCC of tongue) and as literature data is inconclusive in relation to tumorigenic potential there is a need for further longer term data as mentioned in section 3.4. Malignancy is listed in the safety specification of the RMP as an important potential risk.

Tralokinumab has not been studied in pregnant or lactating women, and no information on the excretion of tralokinumab in human milk or effects on the nursing infant is available. There is currently insufficient clinical data available to draw conclusions about the safety of using tralokinumab during pregnancy. Animal studies have not shown any effects on male and female reproductive organs and on sperm count, motility, and morphology. As a precautionary measure, it is preferable to avoid the use of tralokinumab during pregnancy (section 4.6 of SmPC). Use in pregnant and lactating women has been added as a missing information in the list of safety concerns in the RMP. The safety of tralokinumab us in pregnant and lactating women will be monitored in an observational PASS.

3.6. Effects Table

Table 45 Effects Table for tralokinumab AD and exposure pools DLP

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
IGA 0/1 at week 16	Proportion of patients with IGA 0 or 1 at week 16	%	Tralokinumab 300mg Q2W ECZTRA 1: 15.8% ECZTRA 2: 22.2% ECZTRA 3 (+TCS) 38.9%	Placebo ECZTRA 1: 7.1% ECZTRA 2: 10.9% ECZTRA 3: (+TCS) 26.2%	In all studies for the induction period tralokinumab was superior to placebo without or in combination with TCS	Discussion on clinical efficacy (CHMP AR)
EASI 75 at week 16	Proportion of subjects achieving 75% improvement at week 16	%	Tralokinumab 300mg Q2W ECZTRA 1: 25.0% ECZTRA 3: 33.2% ECZTRA 3: (+TCS) 56.0%	Placebo ECZTRA 1: 12.7% ECZTRA 2: 11.4% ECZTRA 3: (+TCS) 35.7%	In all studies for the induction period tralokinumab was superior to placebo without or in combination with TCS	

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
IGA 0/1 at Week 52	IGA of 0/1 at Week 52 among subjects with IGA of 0/1 at Week 16 achieved without rescue medication after initial randomisation to tralokinumab. **Q2W dose regimen**	%	Tralokinumab 300mg Q2W ECZTRA 1: 51.3% ECZTRA 2: 59.3%	Placebo ECZTRA 1: 47.4% ECZTRA 2: 25.0%	Inconsistent results at week 52 – Statistically significant differences only observed in ECZTRA 2	
IGA 0/1 at Week 52	IGA of 0/1 at Week 52 among subjects with IGA of 0/1 at Week 16 achieved without rescue medication after initial randomisation to tralokinumab. **Q4W dose regimen**	%	Tralokinumab 300mg Q4W ECZTRA 1: 38.9% ECZTRA 2: 44.9%	Placebo ECZTRA 1: 47.4 ECZTRA 2: 25.0%	Inconsistent results at week 52 – Statistically significant differences only observed in ECZTRA 2 **Q4W dose regimen less efficacious than Q2W dose regimen**	
EASI-75 at Week 52	EASI-75 at Week 52 among subjects with EASI-75 at Week 16 achieved without rescue medication after initial randomisation to tralokinumab. **Q2W dose regimen**	%	Tralokinumab 300mg Q2W ECZTRA 1: 59.6% ECZTRA 2: 55.8%	Placebo ECZTRA 1: 33.3% ECZTRA 2: 21.4%	Inconsistent results at week 52 – Statistically significant differences only observed in ECZTRA 2	
EASI-75 at Week 52	EASI-75 at Week 52 among subjects with EASI-75 at Week 16 achieved without rescue medication after initial randomisation to tralokinumab. **Q4W dose regimen**	%	Tralokinumab 300mg Q4W ECZTRA 1: 49.1% ECZTRA 2: 51.4%	Placebo ECZTRA 1: 33.3% ECZTRA 2: 21.4%	Inconsistent results at week 52 – Statistically significant differences only observed in ECZTRA 2 **Q4W dose regimen less efficacious than Q2W dose regimen**	
Unfavourable Effects						
Overall Infection rate	Incidence of Infection rate	%	38.0	36.4	Similar overall rate in first 16 weeks of treatment	AD pool Safety analysis Set, adjusted pool

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Overall serious infection		%	0.4	1.1	No tuberculous infection reported in AD trials. Note in the Safety follow up period up to 14 weeks, rate of serious infection: Tralokinumab: 0.4% Placebo: 0.0%	AD pool initial tx and follow up safety analysis set
Viral URTI	Incidence of Viral URTI	%	16.9	11.5	Adjusted: 15.7% vs 12.2%	AD pool safety analysis set
Conjunctivitis	Incidence	%	5.4	1.9		AD pool safety analysis set
Injection Site reactions	Incidence of ISRs	%	3.5	0.3	Mean number of events was higher for tralokinumab after the 1st 4 weeks. Note: one third of ISRs lasted 2-4 days; one third lasted 5+ days	AD pool
Injection Site pain	Incidence	%	2.3	1.7		AD pool
Eosinophilia	Incidence of eosinophilia	%	1.3	0.3	Transient increase in tralokinumab group which returned to baseline over continued treatment	AD pool safety analysis set
Overall malignancy	Overall incidence	%	0.9	0.7	Number of cases of minor skin malignancies, note inclusion of patients with history of local BCC/SCC in clinical trials. Fatal cases of metastatic SCC and cutaneous T cell lymphoma reported in patients treated with tralokinumab. Long term data unavailable.	Simple pooling safety analysis set

Notes: ADRs from the AD initial treatment period are outlined above, it is highlighted that some differences were observed in individual AE reported between AD pivotal trials-EZCTRA1/2 and EZCTRA3.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Efficacy

The analyses of the key efficacy results of all studies especially those for the initial treatment period (Week 0 to Week 16) show a significant higher reduction in severity and symptoms of AD compared to placebo. The primary endpoints (EASI-75 and IGA 0 or 1 at Week 16) were met in all these studies.

The results of secondary endpoints for the initial treatment period supported the primary endpoints results.

Improvements in patients receiving tralokinumab were not only seen in relation to eczematous lesions on the skin but also in relation to other symptoms including pruritus, sleep disturbances (as assessed through the Eczema-related Sleep NRS), anxiety and depression (as assessed through the HADS scores). In addition, the quality of life (as assessed through DLQI) improved in patients treated with tralokinumab.

Therefore, the efficacy of tralokinumab used as monotherapy or in combination with TCS is considered positive. As better efficacy results were reported in the TCS combination trial (ECZTRA 3) as compared to the monotherapy studies, it is recognised that the use of TCS, when appropriate, may provide an additional effect to the overall efficacy of tralokinumab.

It is also recognised that Q4W dose regimen may be less effective than Q2W regimen. However, based on the results on IGA0/1 and EASI75 in the monotherapy pool, efficacy of maintenance treatment with tralokinumab in the Q4W dosing regimen can be accepted. It is at the prescriber's discretion, to recommend every fourth week dosing for patients who achieve clear or almost clear skin after 16 weeks of treatment. In addition, for some subpopulation of patients tapering the dose to every fourth week is not appropriate. The reduced exposure in patients with a high body weight, coupled with the reduced exposure with the Q4W regimen, suggests that the Q4W regimen may not be appropriate for patients with a high body weight.

Safety

The safety profile of tralokinumab was generally well characterised in the first 16 weeks of treatment in the AD population and an acceptable amount of safety data is available from the AD clinical development programme for the initial treatment period.

Much of the safety information up to week 52 is acquired from the majority of patients who were non-responders at week 16 and thus continued tralokinumab Q2W in the open-label fashion. It is apparent that Q4W generally has a more favourable safety profile, however it is acknowledged that more data are available with the higher exposure of Q2W and less with Q4W.

The safety concerns identified in relation to tralokinumab during the safety evaluation of this application relate mainly to infections, eye disorders (conjunctivitis and related conditions) and injection site reactions. These have been reflected in the product information and will be further monitored via routine pharmacovigilance activities and through the ongoing long-term PASS (ECZTEND) listed as category 3 study in the RMP.

Potential concerns in relation to other safety areas were also identified during the procedure, such as limited long term data in patients treated with the proposed dose of tralokinumab Q2W in the long term up to 52 weeks duration, potential concerns relating to malignancy, suicidal ideation/depressive symptoms and cardiovascular events. A number of serious medically important cases in a number of these SOCs were identified in the AD clinical development program. These points have now been adequately addressed by the applicant and will continue to be monitored as part of both routine pharmacovigilance monitoring and through the ongoing long-term PASS (ECZTEND).

Further data on long term safety of tralokinumab in AD will be provided through the PASS (ECZTEND).

3.7.2. Balance of benefits and risks

Efficacy of tralokinumab in the treatment of moderate-to-severe AD in adult patients who are candidates for systemic therapy has been demonstrated.

The risks associated with tralokinumab in the treatment of moderate- to- severe AD in adults have been adequately characterised in the clinical development programme. Overall, based on the data presented the beneficial effects outweigh the unfavourable effects.

3.8. Conclusions

The overall B/R of Adtralza is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Adtralza is favourable in the following indication:

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

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that tralokinumab is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

Appendix

None