# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 761180Orig1s000

# INTEGRATED REVIEW

**Review Memorandum: Adbry (Tralokinumab)**

| | |
|---|---|
| **BLA 761180, SDN 41** | Resubmission (7/2/2021) (Cycle #2)<br>Following FDA Complete Response (4/23/2021) to Cycle #1 review of BLA 761180, SDN 1 initial submission on 4/27/2020 |
| **Clinical Reviewer:** | Hamid Tabatabai, M.D. |
| **Clinical Team Leader:** | David Kettl, M.D. |
| **Project Manager:** | Strother Dixon, Senior Regulatory Health Project Manager |
| **Drug Product:** | Adbry (Tralokinumab) injection (SC), 150 mg/mL |
| **Indication:** | Treatment of moderate to severe Atopic Dermatitis (AD) |
| **Memorandum Date**: | December 22, 2021 |

**Executive Summary**

This application is a Complete Response resubmission of BLA 761180 for tralokinumab-ldrm for the treatment of moderate-to-severe atopic dermatitis (AD) in adult patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. BLA 761180 was initially submitted by LEO Pharma A/S under regulatory pathway 351(a) of the Public Health Service Act on 4/27/2020 and received a Complete Response (CR) letter on 4/23/2021 from the Agency.

Tralokinumab is a new molecular entity, first-in-class, fully human immunoglobulin G4 (IgG4) monoclonal antibody. It is an immunomodulator/interleukin (IL) Inhibitor that neutralizes the cytokine IL-13 by inhibiting its interactions with IL-13 receptors α1 and α2. Other than corticosteroids, tralokinumab is the second systemic product (after dupilumab) to be approved for the treatment of moderate-to-severe AD.

The Phase 3 program included two 52-week placebo-controlled monotherapy trials (ECZTRA-1, ECZTRA-2) and a 32-week trial (ECZTRA-3) evaluating the safety and effectiveness of tralokinumab in combination with topical corticosteroids. the results of the three Phase 3 trials showed statistically significant improvement in the primary endpoints (proportion of subjects with an Investigator's Global Assessment [IGA] score of 0 [clear] or 1 [almost clear] [IGA 0/1] at Week 16 and proportion of subjects with at least 75% reduction in Eczema Area and Severity Index (EASI) score from baseline [EASI-75] at Week 16).

Following completion of the Integrated Review of Marketing Application (Cycle #1), the review team concluded that there was substantial evidence to support the effectiveness of tralokinumab and did not identify safety issues that might impact approval of the application. Agreement on draft labeling was achieved with the sponsor as no safety or efficacy issues were identified by the review team, and no nonclinical or clinical pharmacology issues were identified which would preclude approval of the application.

However, the initial BLA 761180 submission received a Complete Response action as recommended by the Center for Devices and Radiological Health (CDRH) review team, because it did not contain sufficient information regarding the needle-safety performance of the device.

Since the Complete Response action, the applicant resubmitted BLA 761180 on 7/2/2021, including the following deficiencies outlined in the CR letter of 4/23/2021:

- Final finished combination product needle safety performance (testing results for the accessorized pre-filled syringe (APFS) needle safety performance using final finished product after preconditioning over the proposed shelf-life of (b) (4) month to the appropriate confidence and reliability of 95%/99%.
- Data supporting the combination product's shelf-life at BLA approval (the APFS compressive override force testing using (b) (4) month real-time aged samples, and APFS needle safety activation testing using 24-month real-time aged samples), sequentially preconditioned and tested to ensure 95% confidence /99% reliability to support a shelf-life of (b) (4) months at BLA approval. The applicant plans to extend the shelf-life of tralokinumab to 36 months following further similar needle safety performance testing, and accelerated aging to simulate 36 months of real-time storage.

The CDRH review team (ICC review memorandum of 10/13/2021) recommended that the combination product was approvable and no outstanding unresolved information requests or CR deficiencies remained.

Additionally, the Applicant included safety data update (data cut-off date of 3/31/2021) of their initial 120-day safety data update (data cut-off date of 4/30/2020) for the ISS-AD, which was consistent with the safety profile of tralokinumab from the safety review of the initial BLA submission and identified no new safety concerns.

**Pediatrics**

Clinical studies were conducted only in adults. Because tralokinumab is a new active ingredient, this BLA is required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients, under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c).

On 6/28/2018, the Division agreed to the Agreed initial pediatric study plan (Agreed iPSP) submitted by the sponsor on 6/4/2018, which included the following:

- Partial waiver to conduct studies in pediatric patients less than 6 months of age (studies are impossible or highly impractical)
- Deferral of Phase 3 clinical trials in pediatric patients ages 6 months to < 18 years.

On 2/18/2020, the Agency agreed with the sponsor's submitted revised proposed timelines for the pediatric studies to harmonize with the PIP for EMA/PDCO.

During the first review cycle of this BLA, the Pediatric Review Committee (PeRC) agreed to the pediatric study plan presented at the PeRC meeting on 10/27/2020.

**Postmarketing Requirements and Commitment (PMR/PMC)**

The following 6 PMRs and 1 PMC were agreed to by the FDA and the Applicant, and will be issued with the following milestones:

**PMR - 1**
Trial LP0162-1334 (ECZTRA 6) Trial: Efficacy and safety (phase 3, randomized, DB, PC, parallel-group, monotherapy) trial in Adolescents (12 to <18 years of age) with moderate-to-severe atopic dermatitis (AD) who are candidates for systemic treatment.

PMR – 1 Schedule Milestones:
Final Protocol Submission: 06/15/2018
Study/Trial Completion: 03/30/2021
Final Report Submission: 03/30/2022

**PMR – 2**
Trial LP0162-1335: A PK and safety (randomized, single [observer] blinded, parallel-group, monotherapy) dose-ranging trial in pediatric subjects 2 to <12 years of age with moderate-to-severe atopic dermatitis (AD) who are candidates for systemic AD treatment (studied sequentially in 2 cohorts: 6 to <12 years and 2 to <6 years).

PMR – 2 Schedule Milestones:
Final Protocol Submission: 03/31/2022
Study/Trial Completion: 09/30/2025
Final Report Submission: 03/31/2026

**PMR – 3**
Trial LP0162-1336: An efficacy and safety (phase 3, randomized, double-blind, placebo-controlled, parallel-group) trial with tralokinumab and placebo in combination with topical corticosteroid [TCS] therapy in pediatric subjects 2 to <12 years of age with moderate-to-severe atopic dermatitis (AD) who are candidates for systemic AD treatment (studied simultaneously in 2 cohorts: 6 to <12 years and 2 to <6 years).

PMR – 3 Schedule Milestones:
Draft Protocol Submission: 05/31/2023
Final Protocol Submission: 09/30/2023
Study/Trial Completion: 03/31/2027
Final Report Submission: 09/30/2027

**PMR – 4**
Study LP0162-1381: An efficacy, safety, and pharmacokinetic (PK) (phase 2, single-arm, open-label, monotherapy) trial in infants and pediatric subjects (6 months to <2 years of age) with moderate-to-severe atopic dermatitis (AD) who are candidates for systemic AD treatment.

PMR – 4 Schedule Milestones:
Draft Protocol Submission: 02/28/2027
Final Protocol Submission: 06/30/2027
Study/Trial Completion: 12/31/2028

Final Report Submission: 06/30/2029

**PMR – 5**
A prospective, pregnancy exposure registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to tralokinumab during pregnancy to an unexposed control population.

PMR – 5 Schedule Milestones:
Draft Protocol Submission: 06/01/2022
Final Protocol Submission: 10/31/2022
Study/Trial Completion: 09/30/2034
Interim/Other: Not applicable
Final Report Submission: 09/30/2035

**PMR – 6**
An additional pregnancy study that uses a different design from the Pregnancy Registry (for example a retrospective cohort study using claims or electronic medical record data with outcome validation or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to tralokinumab during pregnancy compared to an unexposed control population.

PMR – 6 Schedule Milestones:
Draft Protocol Submission: 06/01/2022
Final Protocol Submission: 10/31/2022
Study/Trial Completion: 06/30/2030
Interim/Other: 06/30/2027
Final Report Submission: 12/30/2030

**PMC – 7**
The applicant commits to conduct a real-time shipping study of commercial product as a Post Marketing Commitment (PMC).

PMC – 7 Schedule Milestones:
Final Report Submission: 07/2022

**Labeling:**
Draft labeling has been agreed to by the Applicant, and the final approved labeling will be attached to the action letter.

Hamid Tabatabai, M.D.
Clinical Reviewer
Division of Dermatology and Dentistry (DDD)
Office of Immunology and Inflammation (OII)
OND/CDER

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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HAMID N TABATABAI
12/22/2021 03:22:19 PM
Clinical Review Memo. for Cycle #2 Approval

DAVID L KETTL
12/22/2021 03:24:37 PM

# Integrated Review

**Table 1. Administrative Application Information**

| Category | Application Information |
|---|---|
| **Application type** | BLA |
| **Application number(s)** | 761180 |
| **Priority or standard** | Standard |
| **Submit date(s)** | 4/27/2020 |
| **Received date(s)** | 4/27/2020 |
| **PDUFA goal date** | 4/27/2021 |
| **Division/office** | Division of Dermatology and Dentistry (DDD) |
| **Review completion date** | 4/19/2021 |
| **Established/proper name** | tralokinumab |
| **(Proposed) proprietary name** | (b) (4) |
| **Pharmacologic class** | IgG4 monoclonal antibody that neutralizes IL-13 cytokine by inhibiting interactions with IL-13 receptors α1 and α2 |
| **Code name** | Click or tap here to enter name. |
| **Applicant** | LEO Pharma A/S |
| **Dosage form(s)/formulation(s)** | Injection |
| **Dosing regimen** | An initial dose of 600 mg (four 150 mg injections), followed by 300 mg (two 150 mg injections) administered every other week. At prescriber's discretion, a dosage of 300 mg every 4 weeks may be considered for patients who achieve clear or almost clear skin after 16 weeks of treatment |
| **Applicant proposed indication(s)/ population(s)** | For the treatment of moderate-to-severe atopic dermatitis in adult patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. TRADENAME can be used with or without topical corticosteroids. |
| **Proposed SNOMED indication** | 24079001 \|Atopic dermatitis (disorder) |
| **Regulatory action** | Complete response |
| **Approved dosage (if applicable)** | NA |
| **Approved indication(s)/ population(s) (if applicable)** | NA |
| **Approved SNOMED term for indication (if applicable)** | NA |

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# Glossary

| | |
|---|---|
| AD | atopic dermatitis |
| ADA | antidrug antibodies |
| AE | adverse event |
| AESI | adverse event of special interest |
| AHR | airway hyperresponsiveness |
| ALT | alanine aminotransferase |
| APFS | accessorized prefilled syringe |
| AR | adverse reaction |
| AST | aspartate aminotransferase |
| AUC | area under the concentration-time curve |
| BILI | bilirubin |
| BLA | biologics license application |
| BMI | body mass index |
| CDER | Center for Drug Evaluation and Research |
| CI | confidence interval |
| CL | clearance |
| $C_{max}$ | maximum concentration |
| $C_{min}$ | minimum concentration |
| CV | cardiovascular |
| DDI | drug-drug interaction |
| DILI | drug-induced liver injury |
| DLQI | Dermatology Life Quality Index |
| EASI | Eczema Area and Severity Index |
| ECG | electrocardiogram |
| ePPND | enhanced prenatal and postnatal development |
| ER | exposure-response |
| FDA | Food and Drug Administration |
| FEI | FDA Establishment Identifier |
| FITC | fluorescein isothiocyanate |
| FMQ | FDA Medical Dictionary for Regulatory Activities query |
| GCP | good clinical practices |
| GD | gestation day |
| GLP | good laboratory practices |
| HLT | high-level term |
| $IC_{50}$ | half-maximal inhibitory concentration |
| ICH | International Council on Harmonisation |
| IGA | Investigator's Global Assessment |
| IgG4 | immunoglobulin G4 |
| IHC | immunohistochemistry |
| IL | interleukin |
| IMP | investigational medicinal product |
| IND | investigational new drug |
| iPSP | initial pediatric study plan |

| | |
|---|---|
| IRB | institutional review board |
| ISS | integrated summary of safety |
| IU | international units |
| IV | intravenous |
| LDH | lactate dehydrogenase |
| $K_D$ | equilibrium dissociation constant |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRHD | maximum recommended human dosage |
| NDA | new drug application |
| NLME | nonlinear mixed effect |
| NOAEL | no observed adverse effect level |
| NRS | numeric rating scale |
| OI | opportunistic infection |
| OPQ | Office of Pharmaceutical Quality |
| OSI | Office of Scientific Investigations |
| PCSV | potentially clinically significant value |
| PD | pharmacodynamic |
| PK | pharmacokinetic |
| PMR | postmarketing requirement |
| popPK | population pharmacokinetics |
| PRO | patient-reported outcome |
| PT | preferred term |
| PYE | patient years of exposure |
| PYFU | patient years of follow-up |
| PYO | patient years of observation |
| Q2W | every 2 weeks |
| Q4W | every 4 weeks |
| qPCR | quantitative polymerase chain reaction |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SC | subcutaneous |
| SCORAD | Scoring Atopic Dermatitis |
| SMQ | Standardized MedDRA Query |
| STEMI | ST segment elevation myocardial infarction |
| SOC | system organ class |
| TCS | topical corticosteroids |
| TEAE | treatment-emergent adverse event |
| ULN | upper limit of normal |
| WRO | written response only |

# I. Executive Summary

## 1. Summary of Regulatory Action

On 4/27/2020 the Applicant (Leo Pharma A/S) submitted a biologics license application (BLA) 761180 for (b) (4) (tralokinumab) for the treatment of moderate-to-severe atopic dermatitis (AD) in adult patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Tralokinumab belongs to the pharmacological class of immunomodulators/interleukin (IL) inhibitors. Tralokinumab is a new molecular entity, first-in-class, fully human immunoglobulin G4 (IgG4) monoclonal antibody that neutralizes the cytokine IL-13 by inhibiting its interactions with IL-13 receptors α1 and α2. If approved, tralokinumab would be the second systemic product (other than corticosteroids), after dupilumab, to be approved for the treatment of moderate-to-severe AD.

The Phase 3 program included two 52-week placebo-controlled monotherapy trials (ECZTRA-1, ECZTRA-2) and a 32-week trial (ECZTRA-3) evaluating the safety and effectiveness of tralokinumab in combination with topical corticosteroids. As set out in Section II.6.2.1, Table 17 (ECZTRA-1 and -2) and Table 18 (ECZTRA-3), the results of the three Phase 3 trials showed statistically significant improvement in the primary endpoints (proportion of subjects with an Investigator's Global Assessment [IGA] score of 0 [clear] or 1 [almost clear] [IGA 0/1] at Week 16 and proportion of subjects with at least 75% reduction in Eczema Area and Severity Index (EASI) score from baseline [EASI-75] at Week 16).

After completing the interdisciplinary analysis and review, the team concluded that there was substantial evidence to support the effectiveness of tralokinumab and did not identify risk issues that might impact approval of the application. Due to the limited information regarding pregnancy impacts, pregnancy registries will be recommended as postmarketing requirements.

A required prelicense inspection, conducted on 3/2/2021 to 3/19/2021 at AstraZeneca Pharmaceuticals LP Frederick Manufacturing Center (FDA Establishment Identifier [FEI] 3002617771), resulted in issuance of a three-item FDA Form 483 and a withhold initial recommendation; however, the Applicant provided an adequate response and the Office of Product Quality determined that the issues had been adequately remedied and has now recommended approval.

There remains an unresolved issue that affects BLA licensure: The application did not contain sufficient information regarding needle-safety performance of the device and the Center for Devices and Radiological Health review team has recommended a Complete Response action.

In view of this outstanding issue, I concur with the Complete Response recommendation of the interdisciplinary review team.

For detailed information, please refer to the reviews included in this Integrated Assessment document and the Product Quality review.

# 2. Benefit-Risk Assessment

## 2.1. Benefit-Risk Framework

**Table 2. Benefit-Risk Framework**

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| **Analysis of Condition** | • AD is a chronic, relapsing, inflammatory cutaneous disorder, which is characterized by intensely pruritic, xerotic skin. Other clinical features may include erythema, edema, erosions, oozing, and lichenification. It is clinically diagnosed and relies principally on disease pattern (morphology and distribution), disease history, and medical history (e.g., personal and/or family history of atopy) (Eichenfield et al. 2014).<br>• Although it may affect all age groups, AD is most common in children. Onset is typically between the ages of 3 and 6 months, with approximately 60% of patients developing the disease during the first year of life and 90% by the age of 5 years. For most patients, the disease resolves by adulthood. However, for 10 to 30% of individuals, AD persists into the adult years, and, for a smaller proportion of subjects, the disease initially presents in adulthood. The prevalence of AD in adults in the United States has been reported (Silverberg and Hanifin 2013) to be 3%, but may be as high as (Chiesa Fuxench et al. 2019) 7.3%.<br>• Comorbidities may include asthma, allergic rhinoconjunctivitis, and food allergies. | • Although AD is not a life-threatening condition, it can be serious. It may significantly impact the quality of life of the patient and family members. Pruritus is a hallmark of the condition and is responsible for much of the disease burden for patients and their families (Weston and Howe 2021). The intense pruritus may disrupt sleep, which can have a carryover effect of tiredness during the day. The dysfunctional skin barrier, further compromised by scratching, may predispose patients to secondary infections. The primary and secondary disease-related skin changes may distort the appearance of the skin. The disease may also impact mood, and affected individuals may experience depression and feelings of social isolation (Drucker et al. 2017). |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| **Current Treatment Options** | • For the Applicant's target population of moderate-to-severe AD, available FDA-approved systemic treatments include dupilumab and corticosteroids.<br>• Phototherapy (narrow-band ultraviolet B as the first-line) is an option for this population, but its drawbacks include a potentially time-intensive, in-office treatment schedule. Risks from phototherapy may vary according to the type of phototherapy and can include actinic damage, sunburn-like reactions, skin cancer (nonmelanoma and melanoma), and cataracts.<br>• Dupilumab is recommended for patients unresponsive to topical therapy for whom phototherapy is not feasible, with concomitant topical corticosteroids as needed.<br>• The American Academy of Dermatology recommends that systemic corticosteroids generally be avoided because of the potential for short- and long-term adverse reactions.<br>• Tacrolimus ointment, 0.1%, is approved for moderate-to-severe AD as a second-line, short-term, noncontinuous chronic treatment for patients unresponsive to other topical treatments.<br>• Systemic products that are used off-label to treat moderate-to-severe AD include cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil[4]. | • In the opinion of this reviewer, approval for licensure of tralokinumab would represent an important addition to the treatment options for patients with moderate-to-severe AD that is not manageable by topical therapies; a population for whom approved treatment options are limited.<br>• Tralokinumab would be the second systemic product approved for treatment of moderate-to-severe AD, following the approval of dupilumab, other than corticosteroids.<br>• Tralokinumab would represent an alternative to dupilumab for systemic treatment of moderate-to-severe AD. Corticosteroids, although approved, are not generally recommended for this indication. |
| **Benefit** | • The efficacy of tralokinumab was demonstrated in two trials, ECZTRA-1 and ECZTRA-2. Tralokinumab was statistically superior to placebo for the primary endpoint of IGA success (defined as scoring 0 or 1) at Week 16, as well as for the secondary endpoints of EASI-75 and pruritus NRS score (i.e., at least a 4-point reduction from baseline in Worst Daily Pruritus NRS score) at Week 16 in all three trials. | • Tralokinumab clearly demonstrated activity in patients with AD in adequate and well-controlled trials.<br>• The clinical trial design and endpoints were appropriate for the AD population, for which there are limited treatment options. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| **Risk and Risk Management** | • The overall assessment of safety of tralokinumab is informed by a variety of sources, including nonclinical toxicology, safety pharmacology studies, and early phase clinical studies. The safety assessment for the intended population of AD subjects is based primarily on the Phase 3 trials.<br>• No deaths were reported during the initial treatment, maintenance, or open-label treatment periods in trial ECZTRA-1, ECZTRA-2, or ECZTRA-3.<br>• The safety database was adequate to assess risks and outcomes. In five AD trials, 1964 subjects were treated with subcutaneous injections of (b) (4) with or without concomitant TCS. A total of 807 subjects was treated with (b) (4) for ≥1 year.<br>• The most common adverse reactions were upper respiratory infections, conjungivitis/keratitis, injection site reactions, and eosinophilia.<br>• In the clinical trials and the vaccine-response trial, the incidence of ADA during the initial 16-week treatment period was 1.4% for subjects treated with (b) (4) 300 mg every other week and 1.3% for subjects treated with placebo. Neutralizing antibodies were seen in 0.1% of subjects treated with (b) (4) and 0.2% of subjects treated with placebo.<br>• Across all trial periods, the ADA incidence for subjects who received (b) (4) was 4.6%, of which 0.9% had persistent ADA and 1.0% had neutralizing antibodies.<br>• No clinically meaningful differences in the pharmacokinetics, safety, or efficacy of tralokinumab-ldrm were observed in patients who tested positive for anti-tralokinumab-ldrm antibody (including neutralizing antibodies). | • Based on the available data, tralokinumab has a favorable safety profile and would be acceptable for approval for licensure of this application upon succcessfully addressing the defiiciencies regarding the needle protection issues identified in the Center for Devices and Radiological Health review and satisfaction of manufacturing inspection issues.<br>• The safety database was adequate for comprehensive safety assessment of tralokinumab for the proposed indication, patient population, dosage regimen, and duration of treatment.<br>• Safety risks have not been identified that require risk management beyond standard pharmacovigilance. A REMS is not recommended for this application.<br>• Due to the limited information regarding pregnancy impacts, pregnancy registries will be recommended as postmarketing requirements. |

Abbreviations: AD, atopic dermatitis; ADA, antidrug antibodies; (b) (4) tralokinumab; EASI-75, at least 75% reduction in Eczema Area and Severity Index score; ECZTRA, ECZema TRAlokinumab; IGA, Investigator's Global Assessment; NRS, numeric rating scale; REMS, risk evaluation and mitigation strategy; TCS, topical corticosteroids

## 2.2. Conclusions Regarding Benefit-Risk

Review of the application supports an approval recommendation for BLA licensure from the nonclinical, clinical pharmacology, clinical, and statistical review teams. Based upon review of all available efficacy and safety data, the benefits of tralokinumab clearly outweigh the risks for treatment of moderate-to-severe AD in adult patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

However, the application did not contain sufficient information regarding needle safety performance of the product, and the recommendation from the Center for Devices and Radiological Health review team is for a Complete Response to this application.

A Discipline review letter was conveyed on 2/11/2021 regarding the assessment of information submitted by the Applicant on the adequacy of needle safety performance testing:

> *"Needle safety performance needs to be tested on the final finished combination product because the prefilled syringe, design differences between your final finished combination product and currently marketed products, combination product manufacturing and preconditioning would impact the performance and reliability. Failure of the needle safety device to perform adequately may result in serious risks (accidental contaminated needle sticks). Provide testing demonstrating that your final finished combination product needle safety performance (needle safety activation and lockout) can meet a confidence and reliability of 95%/99% after aging of the device to the proposed shelf -life, drop testing and simulated shipping per ASTM 4169-16 Standard Practice for Performance Testing of Shipping Containers and Systems sequentially."*

This issue was not able to be resolved during the review cycle despite several interactions with the Applicant and this deficiency is the basis for the recommendation of a Complete Response for the application.

Prior to the PDUFA Goal date, the manufacturing site inspection assessments were completed, and OPQ concluded that the Applicant had adequately addressed the deficiencies previously reported in Form FDA 483 for their manufacturing facility. :

> *"The Office of Pharmaceutical Quality (OPQ), CDER, recommended approval of STN 761180 for* (b) (4) *manufactured by LEO Pharma A/S following completion of assessment and the final determinations of compliance status of the* (b) (4) *(tralokinumab-ldrm) drug substance manufacturing facility.*
>
> *The prelicense inspection was conducted on 03/02 to 03/19/2021 at AstraZeneca Pharmaceuticals LP Frederick Manufacturing Center (FEI 3002617771). A three-item FDA Form 483 was issued and the initial recommendation was withhold. The final classification of the prelicense inspection was completed following the firm's adequate response to objectionable conditions. FDA assessment of the ability of these facilities to conduct manufacturing operations in compliance with current good manufacturing practice was completed, and the final OPQ assessment supports approval of the application."*

# II. Interdisciplinary Assessment

## 3. Introduction

LEO Pharma, Inc. seeks approval for licensure of tralokinumab for the treatment of adult patients with moderate-to-severe atopic dermatitis (AD) whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Tralokinumab would be the second systemic product (other than corticosteroids), after dupilumab, to be approved for the treatment of moderate-to-severe AD. The Applicant conducted three Phase 3 pivotal trials to demonstrate safety and superior efficacy of tralokinumab compared to placebo.

Tralokinumab belongs to the pharmacological class of immunomodulators/interleukin inhibitors. Tralokinumab is a new molecular entity, first-in-class, fully human immunoglobulin G4 (IgG4) monoclonal antibody that neutralizes interleukin (IL)-13 by inhibiting its interactions with IL-13 receptors α1 and α2. Tralokinumab is proposed to be administered by subcutaneous (SC) injection, with or without topical corticosteroids (TCS), at the recommended initial dose of 600 mg followed by 300 mg every 2 weeks (Q2W) (or every 4 weeks [Q4W] for patients who achieve clear or almost clear skin after 16 weeks of treatment).

The review issues with potential impact on the approvability of tralokinumab identified by the review team are summarized in Section 3.1.

### 3.1. Review Issue List

#### 3.1.1. Key Review Issues Relevant to Evaluation of Benefit

##### 3.1.1.1. Key Benefit Review Issue #1

- There were no substantive issues related to the amount, quality, or conclusions regarding the treatment effect of tralokinumab in the studied population.

Dr. Lawrence Parish's site had been terminated by the Applicant during the trial for noncompliance. Due to concerns related to study conduct, potential unblinding, and data integrity and reliability noted during the inspection of Dr. Parish's site (in particular with regard to the Week 16 Eczema Area and Severity Index [EASI] scores), a sensitivity analysis was conducted on data from this site. This was the only site inspected for Protocol LP0162-1326, but did not alter the conclusions regarding efficacy.

### 3.1.2. Key Review Issues Relevant to Evaluation of Risk

#### 3.1.2.1. Key Risk Review Issue #1

- A Discipline review letter was conveyed on 2/11/2021 regarding the assessment of information submitted by the Applicant regarding the adequacy of needle-safety performance testing.

*"Needle safety performance needs to be tested on the final finished combination product because the prefilled syringe, design differences between your final finished combination product and currently marketed products, combination product manufacturing and preconditioning would impact the performance and reliability. Failure of the needle safety device to perform adequately may result in serious risks (accidental contaminated needle sticks). Provide testing demonstrating that your final finished combination product needle safety performance (needle safety activation and lockout) can meet a confidence and reliability of 95%/99% after aging of the device to the proposed shelf-life, drop testing and simulated shipping per ASTM 4169-16 Standard Practice for Performance Testing of Shipping Containers and Systems sequentially."*

This issue was not able to be resolved during the review cycle, and this deficiency is the basis for the recommendation of a Complete Response for the application.

The OPQ, CDER, recommended approval of BLA 761180 for (b) (4) manufactured by LEO Pharma A/S, following the final determination of the compliance status of the (b) (4) (tralokinumab-ldrm) drug substance manufacturing facility. The prelicense inspection was conducted from 3/3/2021 to 3/19/2021 at AstraZeneca Pharmaceuticals LP Frederick Manufacturing Center (FEI 3002617771). A three-item FDA Form 483 was issued, and the initial recommendation was withhold. The final classification of the prelicense inspection is approval, following the Applicant's adequate response to objectionable conditions.

## 3.2. Approach to the Review

Table 3 provides an overview of the clinical trials conducted to support the benefit-risk assessment of tralokinumab for the treatment of moderate-to-severe AD in adult patients. These comprised two identical Phase 3, placebo-controlled, 52-week monotherapy trials (ECZTRA-1 and ECZTRA-2) and one Phase 3, placebo-controlled, 32-week combination therapy with TCS (ECZTRA-3).

The two Phase 2 trials that provided supportive evidence of safety and efficacy for tralokinumab comprised a vaccine response trial (ECZTRA-5) and a dose-finding trial (D2213C00001). The Applicant submitted additional supportive safety data from tralokinumab trials conducted in healthy subjects and in patients with asthma, ulcerative colitis, and idiopathic pulmonary fibrosis.

**Table 3. Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations[1] for Tralokinumab**

| Trial Identifier (NCT#) | Trial Population | Trial Design | Regimen (Number Treated), Duration | Primary and Key Secondary Endpoints | Number of Subjects Planned; Actual Randomized[2] | Number of Centers and Countries |
|---|---|---|---|---|---|---|
| ECZTRA-1<br>NCT03131648 | Adults (≥18 years) with moderate-to severe AD, candidates for systemic therapy:<br>- AD of ≥10% BSA<br>- EASI score ≥12 at screening and ≥16 at baseline<br>- IGA score ≥3<br>- WDP NRS average score ≥4 | Control type:<br>Placebo-controlled<br><br>Randomization:<br>3:1<br><br>Blinding:<br>Double-blind<br><br>Biomarkers:<br>Exploratory<br><br>Innovative design features:<br>PC period: Weeks 0-16.<br>Maintenance period/open-label period Weeks 16-52. | Drug: Tralokinumab<br>Dosage: 600 loading/ 300 maintenance mg<br>Number treated: 602<br>Duration:16 wk | Primary:<br>IGA 0/1 at Week 16<br><br>Secondary:<br>EASI-75 at Week 16 | 780; 802 | 115 sites in five countries:<br>FRA, DEU, JPN, ESP, USA |
| ECZTRA-2<br>NCT03160885 | Same as in ECZTRA-1 | Control type:<br>Placebo-controlled<br><br>Randomization:<br>3:1<br><br>Blinding:<br>Double-blind<br><br>Biomarkers:<br>Exploratory<br><br>Innovative design features:<br>PC period: Weeks 0-16.<br>Maintenance period/open-label period Weeks 16-52. | Drug: Tralokinumab<br>Dosage: 600 loading/ 300 maintenance mg<br>Number treated: 592<br>Duration:16 wk | Primary:<br>IGA 0/1 at Week 16<br><br>Secondary:<br>EASI-75 at Week 16 | 780/794 | 104 sites in nine countries:<br>AUS, CAN, DNK, GBR, ITA, KOR, POL, RUS, USA |

| Trial Identifier (NCT#) | Trial Population | Trial Design | Regimen (Number Treated), Duration | Primary and Key Secondary Endpoints | Number of Subjects Planned; Actual Randomized[2] | Number of Centers and Countries |
|---|---|---|---|---|---|---|
| ECZTRA-3<br>NCT03363854 | Same as in ECZTRA-1, -2 | Control type:<br>Placebo-controlled<br><br>Randomization:<br>2:1<br><br>Blinding:<br>Double-blind<br><br>Biomarkers:<br>Exploratory<br><br>Innovative design features:<br>PC period Weeks 0-16<br>Continuation period Weeks 16-32 | Drug: Tralokinumab<br>Dosage: 600 loading/300 maintenance mg<br>Number treated: 378<br>Duration:16 wk | Primary:<br>IGA 0/1 at Week 16<br><br>Secondary:<br>EASI-75 at Week 16 | 369/380 | 65 sites in eight countries: BEL, CAN, DEU, NLD, POL, ESP, GBR, USA |
| ECZTRA-5<br>NCT03562377 | Adults (18-54 years) with moderate-to-severe AD, candidates for systemic therapy:<br>- AD of ≥10% BSA (SCORAD)<br>- EASI score ≥12 at screening and ≥16 at baseline<br>- IGA score ≥3 | Control type:<br>Placebo-controlled<br><br>Randomization:<br>1:1<br><br>Blinding:<br>Double-blind<br><br>Biomarkers:<br>Exploratory<br><br>Innovative design features:<br>One dose of Tdap and Meningococcal vaccines IM at Week 12 for evaluation of primary endpoints | Drug:<br>Tralokinumab<br>Dosage: 600 loading/300 maintenance mg<br>Number treated: 107<br>Duration:16 wk | Primary:<br>Positive antitetanus response at Week 16<br><br>Positive meningococcal response at Week 16<br><br>Secondary:<br>Click or tap here to enter text. | 200/215 | 46 sites in two countries: CAN and USA |

| Trial Identifier (NCT#) | Trial Population | Trial Design | Regimen (Number Treated), Duration | Primary and Key Secondary Endpoints | Number of Subjects Planned; Actual Randomized[2] | Number of Centers and Countries |
|---|---|---|---|---|---|---|
| D2213C00001<br>NCT02347176 | Adults (18-75 years) with moderate-to severe AD:<br>- AD of ≥10% BSA (EASI)<br>- EASI score ≥12<br>- SCORAD ≥25<br>- IGA score ≥3 | Control type:<br>Placebo-controlled<br><br>Randomization:<br>1:1:1:1<br><br>Blinding:<br>Double-blind<br><br>Biomarkers:<br>Exploratory<br><br>Innovative design features:<br>Dose-finding, combination therapy | Drug:<br>Tralokinumab<br>Dosage: 45, 150, 300 mg<br>Number treated: 153<br>Duration: 12 wk | Primary:<br>Absolute change from baseline in EASI at Week 12<br><br>Percentage of subjects achieving IGA 0 (clear) or 1 (almost clear) and at least a 2-grade reduction from baseline at Week 12 | 184/204 | 55 sites in 6 Countries:<br>AUS, DEU, JPN, POL, CAN, USA |

Source: Clinical Study Report and adsl.xpt; BLA Module 2.7.6, Table 2.
[1] Includes all submitted clinical trials, even if not reviewed in-depth, except for Phase 1 and pharmacokinetic studies.
[2] If no randomization, replace with *Actual Enrolled*
Abbreviations: AD, atopic dermatitis; AUS, Australia; BEL, Belgium; BID, twice daily; BSA, body surface area; CAN, Canada; CTR, clinical trial report; DB, double-blind; DEU, Germany; DNK, Denmark; EASI, Eczema Area and Severity Index; ECZTRA, ECZema TRAlokinumab; ESP, Spain; F, female; FSFV, first subject first visit; GBR, Great Britain; IGA, Investigator's Global Assessment; IM, intramuscularly; IMP, investigational medicinal product; ITA, Italy; KOR, Republic of Korea; JPN, Japan; LSLV, last subject last visit; LTE, long-term extension study; M, male; MC, multicenter; N, number of subjects; NA, not applicable; NCT, National Clinical Trials Registry; NLD, The Netherlands; NRS, numeric rating scale; OL, open-label; PC, placebo-controlled; PG, parallel group; POL, Poland; Q2W, treatment every 2 weeks; R, randomized; RUS, Russia; Q4W, treatment every 4 weeks; SC, subcutaneous injection; SCORAD, Scoring of Atopic Dermatitis; TCS, topical corticosteroid(s); Tdap, combined tetanus, diphtheria, and acellular pertussis vaccine; USA, United States of America; WDP, Worst Daily Pruritis

# 4. Patient Experience Data

Secondary endpoints in ECZTRA-1, -2, and -3 included the following patient-reported outcome assessments (Table 4) during the initial treatment periods from baseline to Week 16:

- Reduction of Worst Daily Pruritus numeric rating scale (NRS) score (weekly average) ≥4 points.
- Change in Scoring Atopic Dermatitis (SCORAD) score, includes both patient-reported and Investigator-reported assessments).
- Change in Dermatology Life Quality Index (DLQI) score.

**Table 4. Patient Experience Data Submitted or Considered**

| **Data Submitted in the Application** | | |
|---|---|---|
| **Check if Submitted** | **Type of Data** | **Section Where Discussed, if Applicable** |
| **Clinical outcome assessment data submitted in the application** | | |
| ☒ | Patient-reported outcome | BLA submission, ISE Section 3.2.2 |
| ☐ | Observer-reported outcome | |
| ☐ | Clinician-reported outcome | |
| ☐ | Performance outcome | |
| **Other patient experience data submitted in the application** | | |
| ☐ | Patient-focused drug development meeting summary | |
| ☐ | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel) | |
| ☐ | Observational survey studies | |
| ☐ | Natural history studies | |
| ☐ | Patient preference studies | |
| ☐ | Other: (please specify) | |
| ☐ | **If no patient experience data were submitted by Applicant, indicate here.** | |
| **Data Considered in the Assessment (But Not Submitted by Applicant)** | | |
| **Check if Considered** | **Type of Data** | **Section Where Discussed, if Applicable** |
| ☒ | Perspectives shared at patient stakeholder meeting | Externally Led PFDD Meeting on Atopic Dermatitis held at College Park Marriott, Hyattsville, MD on 9/23/2019 |
| ☐ | Patient-focused drug development meeting summary report | |
| ☐ | Other stakeholder meeting summary report | |
| ☐ | Observational survey studies | |
| ☐ | Other: (please specify) | |

Abbreviations: BLA, biologics license application; ISE, integrated summary of effectiveness; MD, Maryland; PFDD, patient-focused drug development

# 5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

## 5.1. Clinical Pharmacology Executive Summary

Tralokinumab is a fully human recombinant monoclonal antibody of the IgG4 subclass that specifically neutralizes the IL-13 cytokine by inhibiting its interaction with the IL-13 receptors. The Applicant is developing tralokinumab for the treatment of adult patients with moderate-to-severe AD.

The to-be-marketed tralokinumab drug product is in a liquid formulation at a concentration of 150 mg/mL, supplied as a single-use prefilled syringe to deliver a dose of 150 mg in 1 mL of solution. The same formulation/presentation was used in all clinical studies in this Biologics License Application (BLA) submission and the Applicant has proposed the tralokinumab dosing regimens by subcutaneous injection in adult patients with moderate-to-severe AD below:

- An initial dose of 600 mg (four 150 mg injections), followed by 300 mg (two 150 mg injections) administered Q2W.
- A dosage of 300 mg Q4W may be considered for patients who achieve clear or almost clear skin after 16 weeks of treatment.

This BLA submission consists of 11 clinical studies: 3 Phase 3 studies (ECZTRA-1, ECZTRA-2, and ECZTRA-3), 2 Phase 2 studies (D2213C00001 and ECZTRA-5), and 2 Phase 1 studies (MI-CP224 and CAT-354-0703) in patients with AD. In addition, two Phase 1 studies (CAT-354-0401 and CAT-354-0602) and two Phase 2 studies (MI-CP199 and CD-RI-CAT-354-1049) in patients with asthma.

The clinical pharmacology review focused on the Phase 1, 2, and 3 studies, which assessed the efficacy, safety, and pharmacokinetics (PK) of tralokinumab with or without concomitant TCS in healthy adult subjects or patients with moderate-to-severe AD, as well as population PK (popPK) analyses and exposure-response analyses. The observed PK results and PK simulations in relation to efficacy and safety were used to support the proposed dosing regimens in adult patients with moderate-to-severe AD.

The key review findings with specific recommendations/comments are summarized in Table 5.

**Table 5. Key Review Issues**

| Review Issue | Recommendations and Comments |
|---|---|
| Pivotal or supportive evidence of effectiveness | The efficacy of tralokinumab for the treatment of moderate-to-severe AD was established in three Phase 3 studies (ECZTRA-1, ECZTRA-2, and ECZTRA-3). Exposure-response and PK-PD modeling for efficacy based on data from the Phase 3 studies provide supportive evidence of effectiveness. |
| General dosing instructions | The proposed dosing regimen, an initial dose of 600 mg (four 150 mg injections) followed by 300 mg (two 150 mg injections) administered every other week, is acceptable. Post 16 weeks of treatment, for patients of body weight <100 kg who achieve clear or almost clear skin, a dosage of 300 mg every 4 weeks may be considered; whereas for patients of body weight >100 kg, a dosage of 300 mg every other week may be considered. |
| Dosing in patient subgroups (intrinsic and extrinsic factors) | Dose individualization based on intrinsic or extrinsic factors is not recommended for the initial treatment from weeks 0 to 16; however, post 16 weeks of treatment, for patients of body weight <100 kg who achieve clear or almost clear skin, a dosage of 300 mg every 4 weeks may be considered; whereas for patients of body weight >100 kg, a dosage of 300 mg every other week may be considered. |
| Labeling | The review team has specific content and formatting change recommendations. |
| Immunogenicity | Antibodies to tralokinumab were not associated with clinically relevant changes in serum tralokinumab concentrations and reduced efficacy. |

Abbreviations: AD, atopic dermatitis; ECZTRA, ECZema TRAlokinumab; PD, pharmacodynamic; PK, pharmacokinetic

### 5.1.1. Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in BLA 761180. This BLA is approvable from a clinical pharmacology perspective.

### 5.1.2. Postmarketing Requirement and Commitments

Conduct a PK, safety and efficacy study in subjects 2 to <12 years of age to determine the dose for the Phase 3 study in this population.

Conduct a PK, safety, and efficacy study in subjects 6 months to 2 years of age, with PK assessment conducted early to support dosing.

## 5.2. Summary of Clinical Pharmacology Assessment

### 5.2.1. Pharmacology and Clinical Pharmacokinetics

The PK of tralokinumab was evaluated in healthy subjects and in patients with AD and asthma. A popPK analysis of tralokinumab was conducted using pooled PK data from 10 clinical studies following intravenous (IV) or SC administration. Based on the popPK analysis, body weight was identified as a statistically significant covariate, with steady-state exposure to tralokinumab decreasing with increasing body weight (Table 6).

**Table 6. Summary of General Clinical Pharmacology and Pharmacokinetics**

| Characteristic | Drug Information<br>Pharmacologic Activity |
|---|---|
| Established pharmacologic class | Tralokinumab is an interleukin-13 (IL-13) antagonist. |
| Mechanism of action | Tralokinumab is a human immunoglobulin G4 (IgG4) monoclonal antibody (mAb) that specifically binds to human interleukin-13 (IL-13) and inhibits its interaction with IL-13 receptor α1 and α2 subunits (IL-13Rα1 and α2). IL-13 is a naturally occurring cytokine of the type-2 immune response. Tralokinumab inhibits the bioactivity of IL-13 by blocking its interaction with the IL-13Rα1/IL-4Rα receptor complex. Tralokinumab inhibits IL-13–induced responses, including release of proinflammatory cytokines, chemokines, and IgE. |
| Active moieties | Tralokinumab |
| QT prolongation | mAbs do not require a distinct QT assessment. No clinically relevant changes in vital signs (diastolic blood pressure, systolic blood pressure, pulse rate) or electrocardiogram (ECG) were observed, based on the evaluation of mean values, potentially clinically significant values, and adverse events (AEs). No cardiac safety concerns were observed, based on the centralized ECG evaluation by external cardiovascular ECG experts in the ECZTRA studies. |
| | **General Information** |
| Bioanalysis | Tralokinumab concentrations in human serum were quantified using validated enzyme-linked immunosorbent assay or Gyrolab® sandwich immunoassay approach. These assays, along with related validation reports, were found to be acceptable. |

| Characteristic | Drug Information<br>Pharmacologic Activity |
|---|---|
| Healthy subjects vs. patients | The pharmacokinetic properties of tralokinumab in healthy subjects were generally similar to those in subjects with moderate-to-severe AD. |
| Drug exposure at steady state following the therapeutic dosing regimen (or single dosage, if more relevant for the drug) | Parameter / Mean±standard deviation<br>$AUC_{week4-16}$ 1577.96±529.21 µg day/mL<br>$T_{1/2}$ (b) (4)<br>$C_{avg}$ 113.5±31.3 µg/mL<br>$C_{trough}$ 99.7±42.4 µg/mL |
| Range of effective dosage(s) or exposure | For the primary endpoint, change from baseline in EASI score at Week 12, a statistically significant reduction was observed for both tralokinumab 150 mg and 300 mg Q2W versus placebo, of which 300 mg demonstrated numerically greater reduction than 150 mg, and with no clear safety-related dose-response pattern identified. As such, the 300 mg Q2W dosage was selected and subsequently demonstrated to be an effective dose in the Phase 3 clinical development. |
| Maximally tolerated dosage or exposure | 300 mg is the only dosage tested in ECZTRA studies. Maximally tolerated dosage will be not be applicable. |
| Dosage proportionality | PK of tralokinumab increased in an approximately dose-proportional manner as assessed by AUC and $C_{max}$, across the SC dose range evaluated (45 mg to 600 mg) |
| Accumulation | Based on popPK model simulations, the accumulation ratio of tralokinumab (increase in $C_{max}$ from first dose to steady state) following multiple dosing without a loading dose was predicted to be 2.86. Likewise, the accumulation ratio following multiple dosing with a loading dose was predicted to be 1.43. |
| Time to achieve steady-state | Following 300 mg Q2W dosing (with a 600 mg loading dose), steady state was reached by Week 6, based on the popPK model. |
| Bridge between to-be-marketed and clinical trial formulations | The to-be-marketed tralokinumab drug product is in a liquid formulation at a concentration of 150 mg/mL, supplied as a single-use prefilled syringe to deliver a dose of 150 mg in 1 mL of solution. The same formulation/presentation was used in all clinical studies in this BLA submission. Hence, a bridge between formulations was not needed. |
| | **Absorption** |
| Bioavailability | Tralokinumab was generally well absorbed following SC administration with an absolute bioavailability of 76% based on the popPK analysis. |
| $T_{max}$ | 5-8 days |
| Food effect (fed/fasted) geometric least square mean and 90% CI | This product is administered via subcutaneous injection. Effect of food will not be applicable. |
| | **Distribution** |
| Volume of distribution | A volume of distribution for tralokinumab of approximately 4.2 L was estimated by popPK analysis. |
| Plasma protein binding | N/A |
| Drug as substrate of transporters | Role of transporters was not assessed for this mAb product. |
| | **Elimination** |
| Mass balance results | N/A |
| Clearance | Systemic clearance was estimated to be 0.149 L/day following IV administration. |

| Characteristic | Drug Information<br>Pharmacologic Activity |
|---|---|
| Half-life | Elimination half-life of tralokinumab is estimated to be 3 weeks. |
| Metabolic pathway(s) | Tralokinumab is expected to be metabolized into small peptides by catabolic pathways. |
| Primary excretion pathways (% dosage) | Nonspecific (not target-mediated) elimination by the reticuloendothelial system is expected. |
| | **Intrinsic Factors and Specific Populations** |
| Body weight | The exposure of tralokinumab decreases with increasing body weight. After a 300 mg dose every 4 weeks, the median tralokinumab exposure (AUC) of subjects of body weight >100 kg is expected to be 46% lower than that of subjects weighing <100 kg. Hence, post 16 weeks of treatment, for patients of body weight <100 kg who achieve clear or almost clear skin, a dosage of 300 mg every 4 weeks may be considered; whereas for patients of body weight >100 kg, a dosage of 300 mg Q2W may be considered. |
| Age | Based on the popPK model, age-based dosage adjustment is not needed. |
| Renal impairment | Based on popPK data, no clinically significant differences in the pharmacokinetics of tralokinumab were observed based on mild-to-moderate renal impairment. The effect of severe renal impairment on the pharmacokinetics of tralokinumab is unknown. |
| Hepatic impairment | Based on popPK data, no clinically significant differences in the pharmacokinetics of tralokinumab were observed based on mild hepatic impairment. The effect of moderate-to-severe hepatic impairment on the pharmacokinetics of tralokinumab is unknown. |
| | **Drug Interaction Liability (Drug as Perpetrator)** |
| Inhibition/induction of metabolism | The impact of tralokinumab on cytochrome P450 (CYP450) enzyme activity has not been studied. A clinical drug interaction study (LP0162-1342) is currently ongoing to evaluate the potential effects of tralokinumab on the PK of selected CYP450 substrates in adult patients with moderate-to-severe AD. The Applicant plans to submit the results of this study as a supplement to the BLA in future. |
| Inhibition/induction of transporter systems | The impact of tralokinumab as a transporter inhibitor and inducer has not been studied and not considered necessary. |
| | **Immunogenicity (if Applicable)** |
| Bioanalysis | ADA in serum was assessed with an ADA assay using a three-tiered testing approach consisting of validated screening, confirmatory, and titering steps. In the ECZTRA (Phase 3 in AD) and STRATOS (Phase 3 in asthma) studies, serum samples with confirmed positive ADA were also tested for nAb using an nAb assay. |
| Incidence | In the ECZTRA studies, the ADA incidence was similar in subjects treated with tralokinumab (1.4%) and placebo (1.3%) during the initial 16-week treatment period. Furthermore, only 0.1% of tralokinumab-treated subjects and 0.2% of placebo-treated subjects had treatment-emergent nAb during the initial 16 weeks of treatment. In addition, the ADA and nAb incidence after 16 weeks of treatment was low and similar for tralokinumab and placebo, confirming the low immunogenicity potential of tralokinumab. |
| Clinical impact | No distinct pattern of AEs was found in subjects who were positive for ADA or nAb, and no increased risk of anaphylaxis, serious allergic reactions, immune-complex disease, serum sickness, or serum sickness-like reactions was identified in the ADA ECZTRA analysis set. There was generally no indication of any impact of ADA or nAb on PK or efficacy. |

Abbreviations: AD, atopic dermatitis; ADA, antidrug antibody; AUC, area under the concentration–time curve; BLA, biologics license application; $C_{avg}$, average concentration; $C_{max}$, maximum concentration; $C_{trough}$, trough concentration; EASI, Eczema Area and Severity Index; ECZTRA, ECZema TRAlokinumab; NA, not applicable; nAb, neutralizing antibody; PK, pharmacokinetics; popPK, population PK; Q2W, every 2 weeks; SC, subcutaneous; $T_{1/2}$, terminal half-life

## 5.2.2. Clinical Pharmacology Questions

### Does the Clinical Pharmacology Program Provide Supportive Evidence of Effectiveness?

Yes. The overall Phase 3 efficacy results provide evidence that tralokinumab is effective for the treatment of adult patients with moderate-to-severe AD. The exposure-response relationships for Investigator's Global Assessment (IGA) 0/1 and EASI-75 provide supportive evidence of effectiveness.

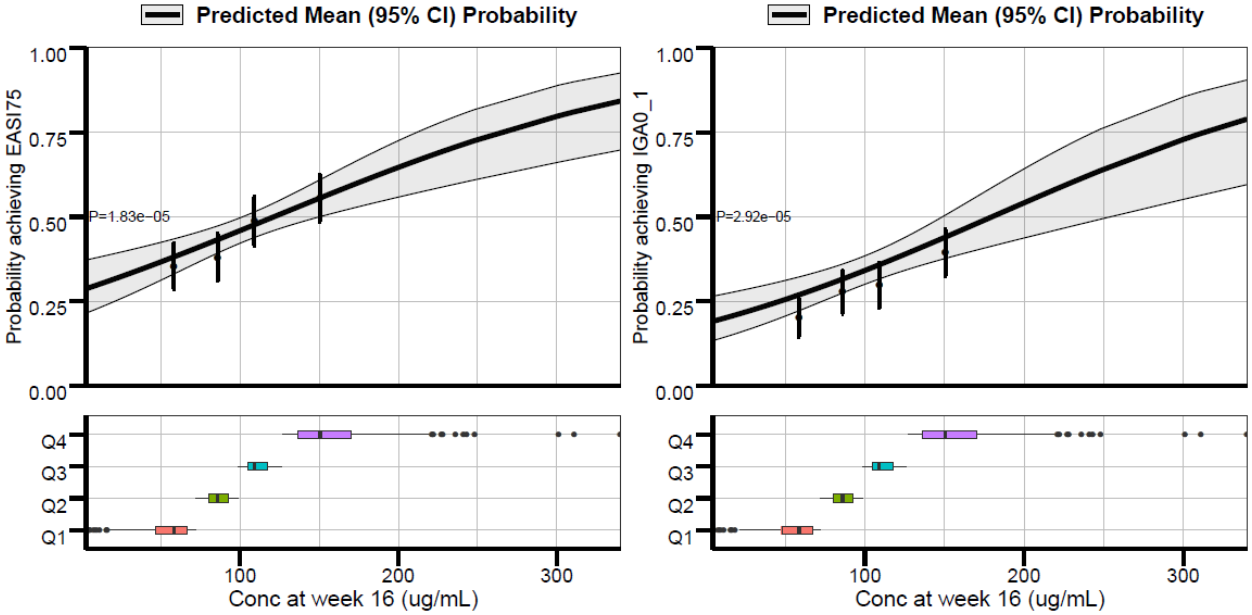
**Dose-Response for Efficacy in Phase 3 Studies**

Because only one dose was studied in the Phase 3 trials, a dose-response analysis cannot be conducted. The efficacy results from the Phase 3 trials are summarized in Section 6.

**Exposure-Response for Efficacy**

Positive exposure-response relationships were observed for efficacy in terms of EASI-75 and IGA 0/1 at Week 16 based on the logistic regression analyses conducted by the reviewer utilizing data from the pivotal Phase 3 studies (Figure 1), which suggest that potentially efficacy could further improve with higher exposure (or higher dose). However, given that the exposure-response analyses were based on data with a single dose level, the observed exposure-response relationships could be confounded and should be interpreted with caution.

**Figure 1. Logistic Regression Relating Probability of Achieving EASI-75 (Left) and IGA (0,1) (Right) With Tralokinumab Trough Concentration at Week 16 in Patients With Moderate-to-Severe AD**




Source: Reviewer's analysis.
Mean regression line—black, confidence area around regression line—grey. The p-value represents the statistical significance of the inclination of the regression line. Means of response variables (black circles) and confidence intervals (black vertical lines) around the means are presented in the figures by quartile of exposure.
Abbreviations: AD, atopic dermatitis; conc, concentration; EASI-75, at least 75% reduction in Eczema Area and Severity Index score; IGA, Investigator's Global Assessment

## Is the Proposed Doing Regimen Appropriate for the General Patient Population for Which the Indication is Being Sought?

The Applicant proposed a dosing regimen of 300 mg Q2W following a loading dose of 600 mg for the initial treatment (Weeks 0 to16), and the Agency proposed 300 mg Q2W for subjects of body weight >100 kg as well as 300 mg Q4W for subjects of body weight <100 kg at the maintenance treatment stage (post Week 16). These appear appropriate for the general patient population for which the indication is being sought.

### Phase 3 Dose Selection

The Applicant conducted a Phase 2b (D2213C00001) trial to evaluate three SC doses of tralokinumab, namely 45 mg, 150 mg, and 300 mg (Q2W), versus placebo in adults with moderate-to-severe AD. Although all three doses were efficacious and had similar acceptable safety profiles, the 300 mg dose demonstrated numerically higher efficacy and a lack of a safety-related dose-response, and was therefore selected for continued Phase 3 development.

### Dose-Response for Efficacy in Phase 3 Studies

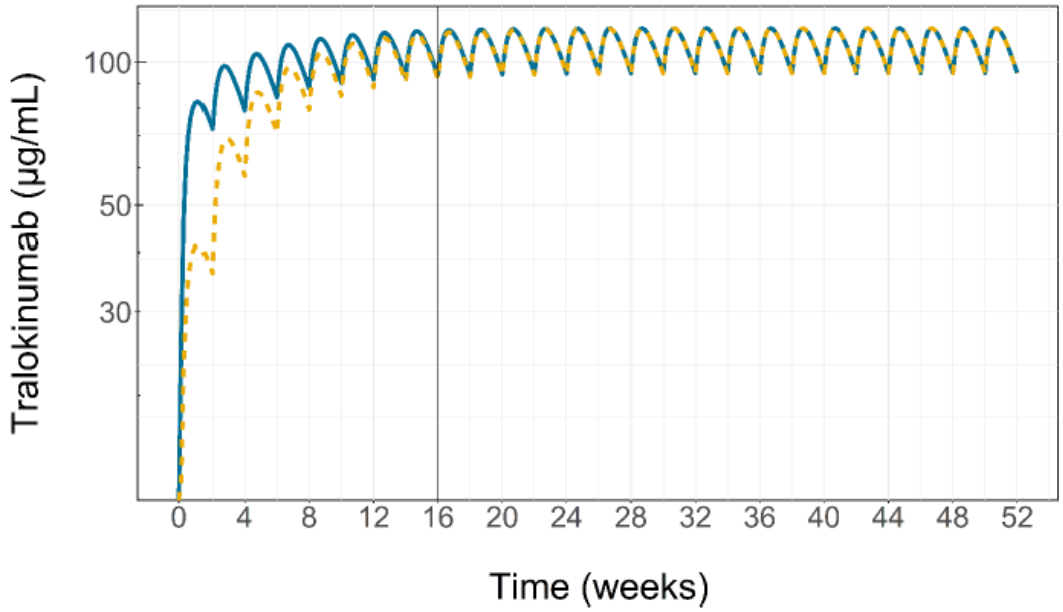
In the Phase 3 studies, ECZTRA-1, -2, and -3, a dose-response relationship for efficacy was observed for IGA 0/1 and EASI-75 at Week 16. In addition, all primary and secondary endpoints at Week 16 were met (Section 6.2.5.1, Table 17). Therefore, superiority of tralokinumab Q2W over placebo was demonstrated, both when tralokinumab was used as monotherapy (ECZTRA-1 and -2) and in combination with TCS (ECZTRA-3). See Section 6 for the clinical and biostatistics evaluation and details of the design and results of the Phase 3 studies.

The observed positive exposure-efficacy relationships support the proposed dosing regimen of 300 mg Q2W, the highest dose level tested in clinical efficacy trials (Figure 1).

### Impact of Loading Dose

A loading dose of 600 mg was administered in the Phase 3 studies to enable systemic concentrations of tralokinumab to reach steady state more rapidly. Based on the popPK simulations, steady state (90% of steady state) was reached at Week 6 with a loading dose and at Week 10 without a loading dose (Figure 2). Furthermore, serum concentrations after a 600 mg loading dose were predicted not to exceed those at steady state for tralokinumab 300 mg Q2W in subjects with AD, which was confirmed by the observed trough concentrations of tralokinumab after the loading dose in ECZTRA-1, -2, and -3.

**Figure 2. Pharmacokinetic Simulation of Typical Population Values for Tralokinumab Serum Concentration With and Without a Loading Dose**




Source: Panel 19. 2.7.2 Summary of Clinical Pharmacology.

**Dosing Regimen in the Maintenance Treatment Period**

Further evaluation of tralokinumab 300 mg Q4W from Week 16 onwards in ECZTRA-1, -2, and -3 was conducted to establish whether less frequent dosing of tralokinumab is sufficient for long-term maintenance of efficacy. The improvements in the extent and severity of AD skin lesions observed after 16 weeks of tralokinumab treatment were maintained at Week 52 in more than half of the applicable responders with both the Q2W and the Q4W monotherapy dosing regimens as compared to placebo, indicating a sustained clinical response to tralokinumab beyond Week 16 in the maintenance treatment. See Section 6 for Clinical and Biostatistics evaluation and details of the study design and results of the Phase 3 studies.

Additional popPK simulations were conducted to demonstrate that in the maintenance treatment, maintaining a dosage of 300 mg Q2W is recommended for subjects of body weight >100 kg, whereas a dosage of 300 mg Q4W for subjects of body weight <100 kg may be considered (Figure 4). See the responses to the question below for details.

**Safety Considerations**

Based on an evaluation of the AE summaries (overall incidence, event number/rate, causality, severity, and seriousness) and the AE distribution by system organ class (SOC) and preferred term (PT) in the initial treatment period (monotherapy pool), there were no clear differences in the safety profile of tralokinumab across body weight categories at the dosing regimen of 300 mg Q2W in the initial treatment period. Furthermore, the types and rates of AEs and SAEs were comparable across the treatment groups. See Section 7 for additional safety information. There was generally no indication of an impact of antidrug antibodies (ADA) or nAb on PK or efficacy.

Overall, the proposed dosing regimen is supported by the efficacy and safety results in pivotal Phase 3 studies. Refer to Sections 6 and 7 for Clinical and Biostatistics evaluation and details.

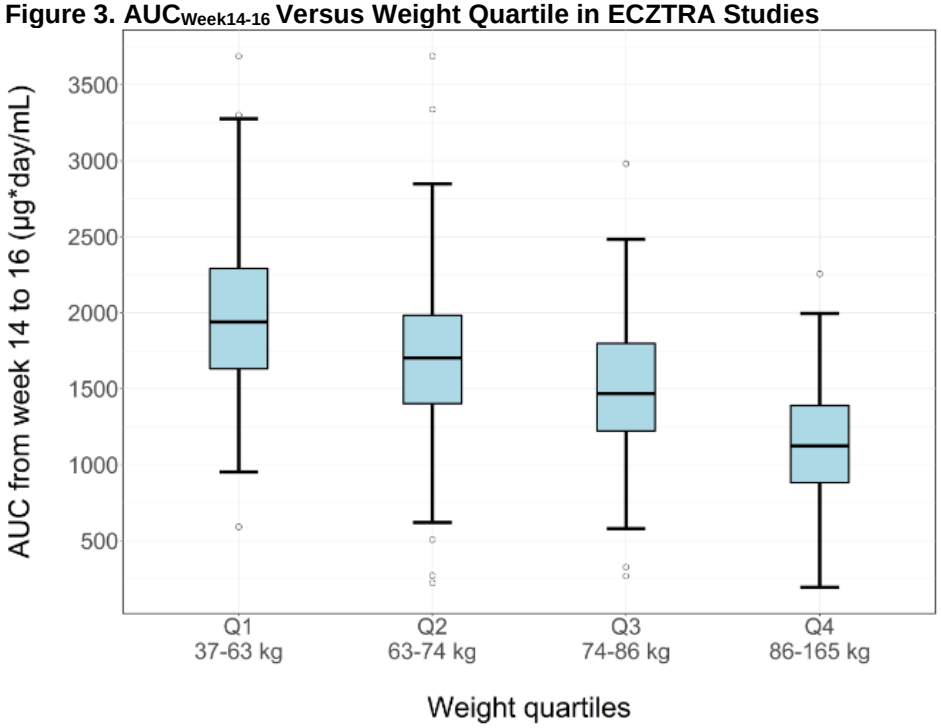
## Is an Alternative Dosing Regimen or Management Strategy Required for Subpopulations Based on Intrinsic Patient Factors?

Subgroup analyses by body weight in Phase 3 studies did not indicate a significant efficacy difference at Week 16 between light and heavy subjects, although significantly lower exposures were observed in subjects of body weight >100 kg. Therefore, a dose adjustment based on body weight is not recommended for the initial treatment from Weeks 0 to 16 at a dose of 300 mg Q2W following a loading dose of 600 mg. However, based on the expected lower exposure in heavy subjects, the potential positive exposure-efficacy relationship, and the limited observed data in the maintenance phase (post 16 weeks of treatment), the dosing frequency should be maintained at Q2W for subjects of >100 kg body weight, while for subjects of <100 kg body weight, the dosing frequency may be changed to Q4W.

### Effect of Body Weight on PK

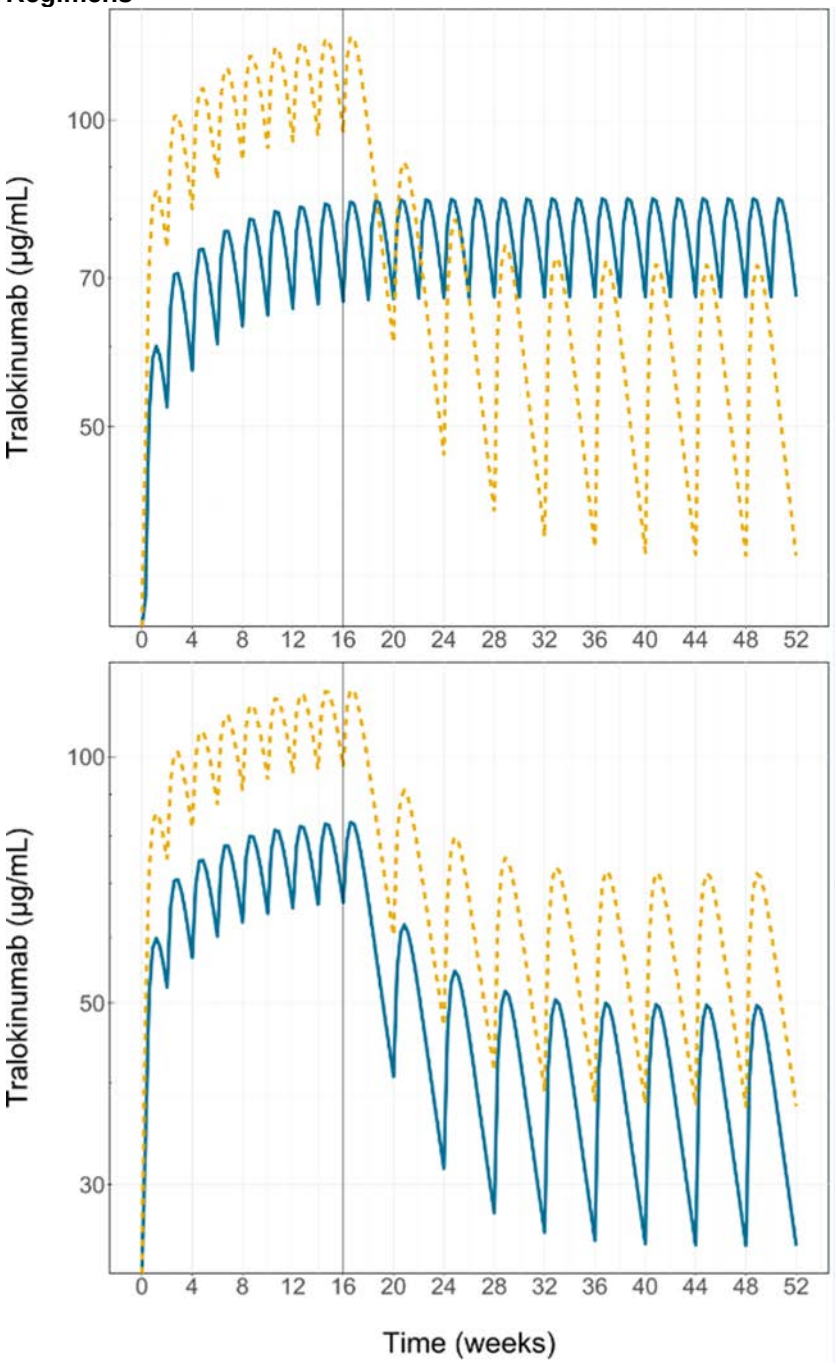
Based on the established tralokinumab popPK model, body weight was identified as a significant covariate that influences tralokinumab exposure in adult patients with moderate-to-severe AD. The exposure of tralokinumab decreases with increasing body weight (Figure 3). PopPK model-based simulations were conducted to investigate the tralokinumab PK profiles for subjects with typical body weights at varying dosing regimens (Figure 4). The tralokinumab exposure (area under the concentration-time curve [AUC]) of a typical subject with a body weight of 111 kg, which represents subjects weighing >100 kg, is expected to be 1.46-fold lower than that of a typical subject with a body weight of 72 kg, which represents subjects weighing <100 kg. As such, post 16 weeks of treatment, maintaining a dosage of 300 mg Q2W is recommended for subjects of body weight >100 kg. The resulting AUC of a subject with a typical high body weight of 111 kg following 300 mg Q2W is expected to be 1.37-fold higher than that of a subject with a typical low body weight of 72 kg following 300 mg Q4W. As such, post 16 weeks of treatment, in subjects weighing >100 kg, the dosing frequency should be maintained at Q2W, whereas in subjects weighing <100 kg, the dosing frequency should be changed to Q4W.

**Figure 3. $AUC_{Week14-16}$ Versus Weight Quartile in ECZTRA Studies**




Source: Reviewer's analysis to confirm Panel 15 in the Applicant's Population Pharmacokinetics report.
Abbreviations: $AUC_{Week14-16}$, area under the concentration–time curve from week 14 to 16; ECZTRA, ECZema TRAlokinumab; Q, quarter

**Figure 4. Simulations of Tralokinumab PK for Subjects of Typical Bodyweight at Varying Dosing Regimens**




Source: Reviewer's independent analysis.
Top: Simulations of the concentration–time profiles of a typical subject (weight 111 kg, solid blue line) following tralokinumab 300 mg Q2W for 52 weeks and another typical subject (weight 72 kg, yellow dashed line) with tralokinumab 300 mg Q2W for 16 weeks followed by tralokinumab 300 mg Q4W until Week 52.
Bottom: Simulations of the concentration–time profile for a typical subject (weight 111 kg, solid blue line) and another typical subject (weight 72 kg, yellow dashed line) dosed with tralokinumab 300 mg Q2W for 16 weeks followed by tralokinumab 300 mg Q4W until Week 52.
Abbreviations: PK, pharmacokinetics; Q2W, every 2 weeks; Q4W, every 4 weeks

## Effect of Body Weight on Efficacy

Body weight was not identified to be a significant covariate impacting tralokinumab efficacy in adult patients with moderate-to-severe AD in the pivotal Phase 3 studies. This was based on the exposure-response (nonlinear mixed effect) analysis (model-predicted $AUC_{0\text{-}W16}$ as the independent variable and ΔEASI% as the response variable) and the logistic regression modeling (observed $C_{trough}$ at Week 16 as the independent variable and probability of patients achieving an IGA 0/1 or EASI-75 as response variables).

A brief investigation was conducted by the statistical reviewer on efficacy differences stratified by body weight category (Week 52 for ECZTRA-1, -2; Week 32 for ECZTRA-3) between the Q2W and Q4W dosing regimens in the maintenance treatment. The results (Table 7) indicated that subjects of body weight >100 kg showed numerically better efficacy with Q2W dosing compared to Q4W dosing. Because the sample size of subjects of body weight >100 kg who maintained a response at Week 52 was very small, the efficacy results for this subgroup are considered exploratory and not fully reliable.

**Table 7. Proportion of Subjects who Maintained a Response at Week 52 by Weight Category in the Pivotal Phase 3 Studies (ECZTRA-1, ECZTRA-2, and ECZTRA-3)**

| | ECZTRA 1 | | | | |
|---|---|---|---|---|---|
| | Tralokinumab Q2W | Tralokinumab Q4W | Placebo | Q2W - Placebo | Q4W - Placebo |
| **IGA 0/1** | **N=39** | **N=36** | **N=19** | | |
| <100 mg (N=35, 33, 17) | 46% | 41% | 33% | 11% | 8% |
| >=100 mg (N=4, 3, 2) | 100% | 100% | 100% | 0% | 0% |
| **EASI 75** | **N=47** | **N=57** | **N=30** | | |
| <100 mg (N=41, 54, 27) | 58% | 46% | 30% | 28% | 16% |
| >=100 mg (N=6, 3, 3) | 67% | 100% | 67% | 0% | 33% |

Source: Statistical Reviewer's Analysis
[1] Maintenance analysis set (MAS) defined as all subjects who received tralokinumab in the initial treatment period and who were re-randomized to maintenance treatment; subjects who were not exposed to maintenance treatment were excluded.
Subjects who received rescue medication or were transferred to open-label treatment were considered non-responders. Missing data at Week 52 were imputed using the non-responder imputation (NRI) method

| | ECZTRA 2 | | | | |
|---|---|---|---|---|---|
| | Tralokinumab Q2W | Tralokinumab Q4W | Placebo | Q2W - Placebo | Q4W - Placebo |
| **IGA 0/1** | **N=54** | **N=49** | **N=28** | | |
| <100 mg (N=49, 45, 25) | 61% | 47% | 28% | 33% | 19% |
| >=100 mg (N=5, 4, 3) | 40% | 25% | 0% | 40% | 25% |
| **EASI 75** | **N=77** | **N=74** | **N=41** | | |
| <100 mg (N=70, 67, 37) | 57% | 51% | 24% | 33% | 27% |
| >=100 mg (N=7, 7, 4) | 43% | 0% | 0% | 43% | 0% |

Source: Statistical Reviewer's Analysis; Sites 423 and 435 from Trial ECZTRA 2 were **NOT** removed.
[1] Maintenance analysis set (MAS) defined as all subjects who received tralokinumab in the initial treatment period and who were re-randomized to maintenance treatment; subjects who were not exposed to maintenance treatment were excluded.
Subjects who received rescue medication or were transferred to open-label treatment were considered non-responders. Missing data at Week 52 were imputed using the non-responder imputation (NRI) method

| | ECZTRA 3 | | | | |
|---|---|---|---|---|---|
| | Tralokinumab Q2W + TCS | Tralokinumab Q4W + TCS | Placebo + TCS | Q2W - Placebo | Q4W - Placebo |
| **IGA 0/1** | **N=48** | **N=49** | **N=33** | | |
| <100 mg (N=40, 44, 30) | 90% | 77% | 63% | 27% | 14% |
| >=100 mg (N=8, 5, 3) | 87% | 80% | 33% | 54% | 47% |
| **EASI 75** | **N=67** | **N=65** | **N=40** | | |
| <100 mg (N=55, 52, 35) | 94% | 90% | 83% | 11% | 7% |
| >=100 mg (N=12, 7, 5) | 83% | 100% | 40% | 43% | 60% |

Source: Statistical Reviewer's Analysis; Site 818 was **NOT** removed.
[1] Continuation treatment analysis set was defined as all randomized subjects who did not withdraw from the trial before or at the Week 16 visit and who were exposed to at least 1 dose of IMP in the continuation treatment period. Missing data at Week 32 were imputed using the non-responder imputation (NRI) method.

Source: Statistical Reviewer's Analysis
Abbreviations: EASI75, at least 75% reduction in Eczema Area and Severity Index score; ECZTRA, ECZema TRAlokinumab; IGA, Investigator's Global Assessment; IMP, investigational medicinal product; Q2W, every 2 weeks; Q4W, every 4 weeks; TCS, topical corticosteroids

## What is the Overall Incidence of Immunogenicity to Tralokinumab? What is the Impact of Immunogenicity on PK and Efficacy?

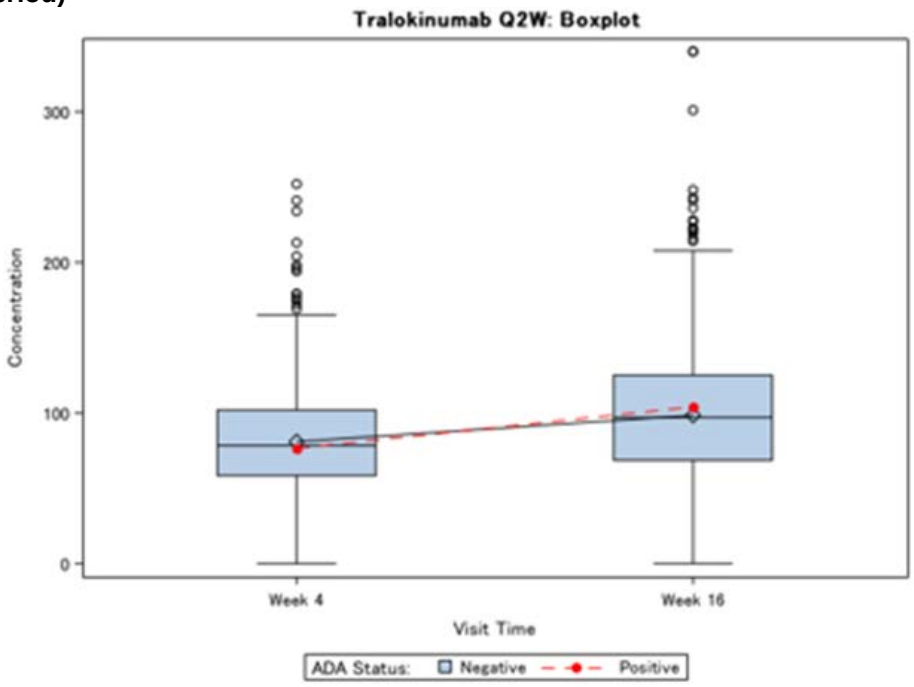
### Immunogenicity Incidences for ADA and Neutralizing ADA

The immunogenicity data presented in this application suggest that tralokinumab treatment does not increase the occurrence of immunogenicity. The rate of ADAs was low in all clinical studies with tralokinumab. During the initial 16 weeks of treatment in the ECZTRA studies, the ADA incidence was low in subjects treated with tralokinumab (1.4%) and few subjects had treatment-emergent nAb (tralokinumab: 2/1,553 subjects, 0.1%. The ADA and nAb incidence after 16 weeks of treatment was low and similar for tralokinumab and placebo, confirming the low immunogenicity of tralokinumab.

### Immunogenicity Impact on PK

Overall, there was no apparent difference in the mean tralokinumab serum concentration between ADA-positive and ADA-negative subjects initially randomized to tralokinumab in the ADA ECZTRA analysis set during the initial treatment period (Figure 5). Therefore, based on the mean tralokinumab serum concentrations, there was no indication of an overall impact of ADA on the PK of tralokinumab.

**Figure 5. Tralokinumab Concentration of ADA-Positive and -Negative Subjects (Q2W, Initial Treatment Period)**



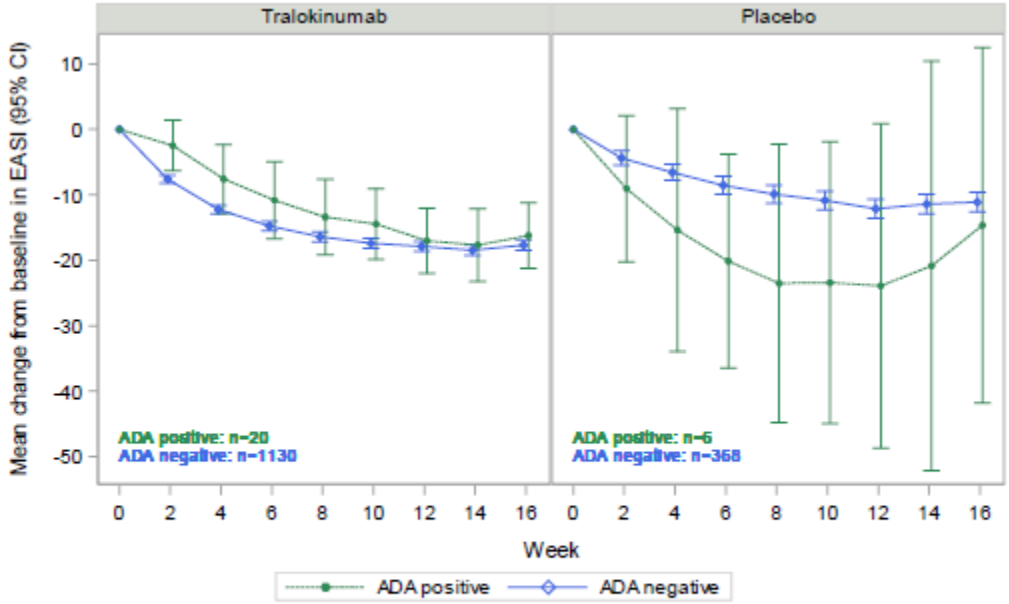

Source: Office of Clinical Pharmacology Frontload analyst's analysis.
Abbreviations: ADA, antidrug antibody; Q2W, every 2 weeks

## Immunogenicity Impact on Efficacy

The responder rates in ADA-positive and -negative subjects at Week 16 according to both IGA 0/1 and EASI-75 indicated no apparent overall loss of efficacy due to the presence of ADA. The same trend was observed for the open-label treatment period.

The mean reduction in the EASI score from baseline to Week 16 was similar for ADA-negative and -positive subjects, further supporting that there was no impact of ADA on efficacy (Figure 6). Similar trends were observed for the entire treatment period.

**Figure 6. Change in EASI by ADA Status, Initial Treatment Period: Monotherapy Pool**




All observed data included. Descriptive CIs based on data from each separate visit.
ADA: Anti-drug antibodies, EASI: Eczema Area and Severity Index, CI: Confidence interval.
ADA positive: At least one positive post-baseline ADA response during initial period.
ADA negative: All post-baseline ADA assessments negative during initial period.

Source: Panel 16. 5.3.5.3. Summary-Immunogenicity-isi-ada-ecztra.

No distinct pattern of AEs was found in subjects who were positive for ADA or nAb, and no increased risk of anaphylaxis, serious allergic reactions, immune-complex disease, serum sickness, or serum sickness-like reactions was identified in the ADA ECZTRA analysis set. There was generally no indication of any impact of ADA or nAb on PK or efficacy. See Section 6 for additional efficacy information.

Together, these results demonstrate a low immunogenic potential of tralokinumab and no apparent impact on the clinical benefit-risk profile of this treatment.

## Nonclinical Assessment of Potential Effectiveness

The nonclinical data support the potential effectiveness of tralokinumab based on the findings described below. Refer to Section III.13 for details.

Tralokinumab had a strong affinity for human IL-13, with an equilibrium dissociation constant ($K_D$) of 58pM, and dose-dependently inhibited IL-13 from interacting with IL-13Rα1 and IL-13Rα2. In vitro studies showed that tralokinumab inhibited the effects of human IL-13 in a range of primary cell-based assays (e.g., TF-1 cell proliferation, expression of CD23 and VCAM-1, release of eotaxin, eosinophil shaping and chemotaxis, and potentiation of $Ca^{2+}$-signaling histamine bronchial smooth-muscle contraction). In vivo, tralokinumab inhibited or decreased the following responses involving IL-13: eosinophil influx and/or airway hyperresponsiveness, elevated serum IgE level, and the response to antigen in sensitized cynomolgus monkeys.

# 6. Assessment of Effectiveness

## 6.1. Dose and Dose Responsiveness

The Applicant conducted three Phase 3 trials, ECZTRA-1, ECZTRA-2, and ECZTRA-3. ECZTRA-1 and ECZTRA-2 were monotherapy trials, whereas ECZTRA-3 was a combination therapy trial that allowed the use of TCS.

The proposed dose was determined to be acceptable for approval.

## 6.2. Clinical Trials Intended to Demonstrate Efficacy

### 6.2.1. Trial Design

#### ECZTRA-1 and ECZTRA-2

The monotherapy trials were two identically designed, randomized, multicenter, double-blind, placebo-controlled, Phase 3 trials (ECZTRA-1 and ECZTRA-2) to evaluate the efficacy and safety of tralokinumab monotherapy in adult subjects with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Design schematics for the monotherapy trials are provided in Figure 7. The protocols specified enrollment and randomization of approximately 780 subjects from approximately 130 sites at a 3:1 ratio to receive tralokinumab 300 mg (N=585) or placebo (N=195) Q2W. Randomization was stratified by region (ECZTRA-1: North America, Europe and Japan; ECZTRA-2: North America, Europe, Australia, and Asia) and baseline disease severity (IGA of 3 or 4).

The trials consisted of a screening period (2 to 6 weeks), a 16-week initial treatment period (Week 0 to Week 16), a 36-week maintenance treatment period (Week 16 to Week 52), and a 16-week off-treatment safety follow-up period (Week 52 to Week 66). Subjects had clinic visits at baseline, screening, and every other week thereafter until Week 52. A follow-up visit was conducted at Week 66. At baseline (Day 0), each subject received four SC injections of 150 mg tralokinumab or placebo, for a total loading dose of 600 mg. At subsequent visits, each subject received two SC injections of 150 mg tralokinumab or placebo (Q2W), for a total dose of 300 mg. See Section III.15 for a more complete description of the Phase 3 trials.

#### ECZTRA-3

ECZTRA-3 was a randomized, multicenter, double-blind, placebo-controlled, Phase 3 trial to confirm the efficacy and safety of tralokinumab as adjunct therapy with TCS in adult subjects with moderate-to-severe AD who are candidates for systemic therapy.

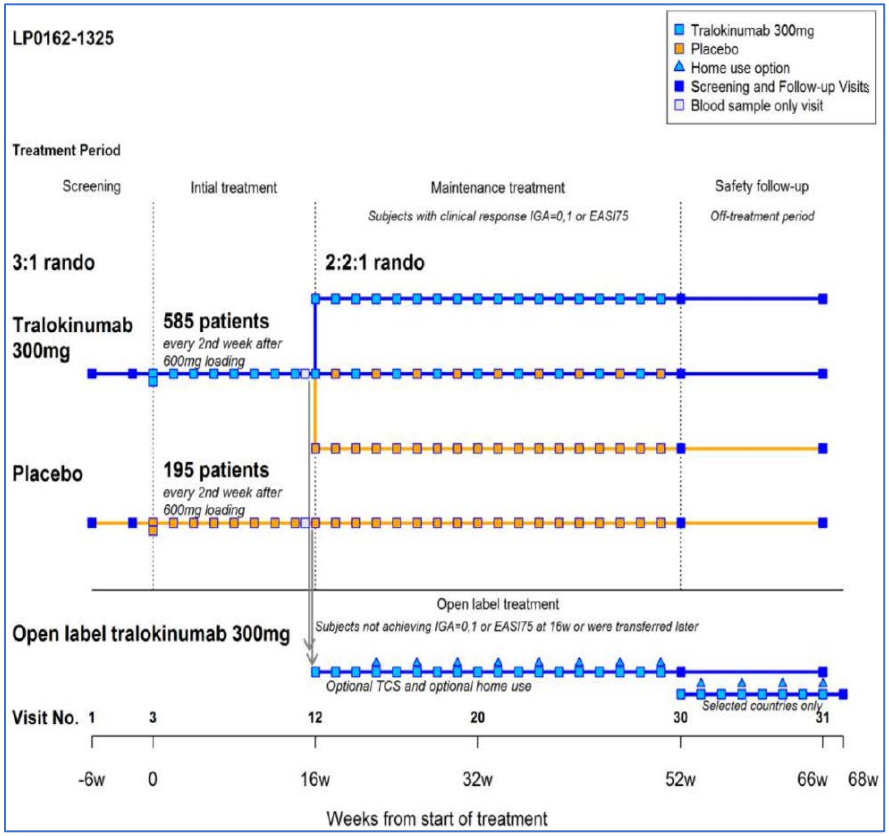
A trial design schematic is presented in Figure 8. The protocol specified enrollment and randomization of approximately 369 subjects from approximately 70 sites in Europe and North America at a 2:1 ratio to tralokinumab 300 mg+TCS (N=246) or placebo+TCS (N=123) Q2W.

Randomization was stratified by region (North America and Europe) and baseline disease severity (IGA of 3 or 4).

The trial consisted of a screening period (2 to 6 weeks), a 16-week initial treatment period (Week 0 to Week 16), a 16-week continuation treatment period (Week 16 to Week 32), and a 14-week off-treatment follow-up period for the assessment of safety (Week 32 to Week 46). Subjects had clinic visits at baseline, screening, and every other week thereafter until Week 52. A follow-up visit was conducted at Week 66. At baseline, each subject received four subcutaneous injections of 150 mg tralokinumab or placebo, for a total loading dose of 600 mg. At subsequent visits, each subject received two SC injections of 150 mg tralokinumab or placebo (Q2W), for a total dose of 300 mg. See Section III.15 for a more complete description of the Phase 3 trials.

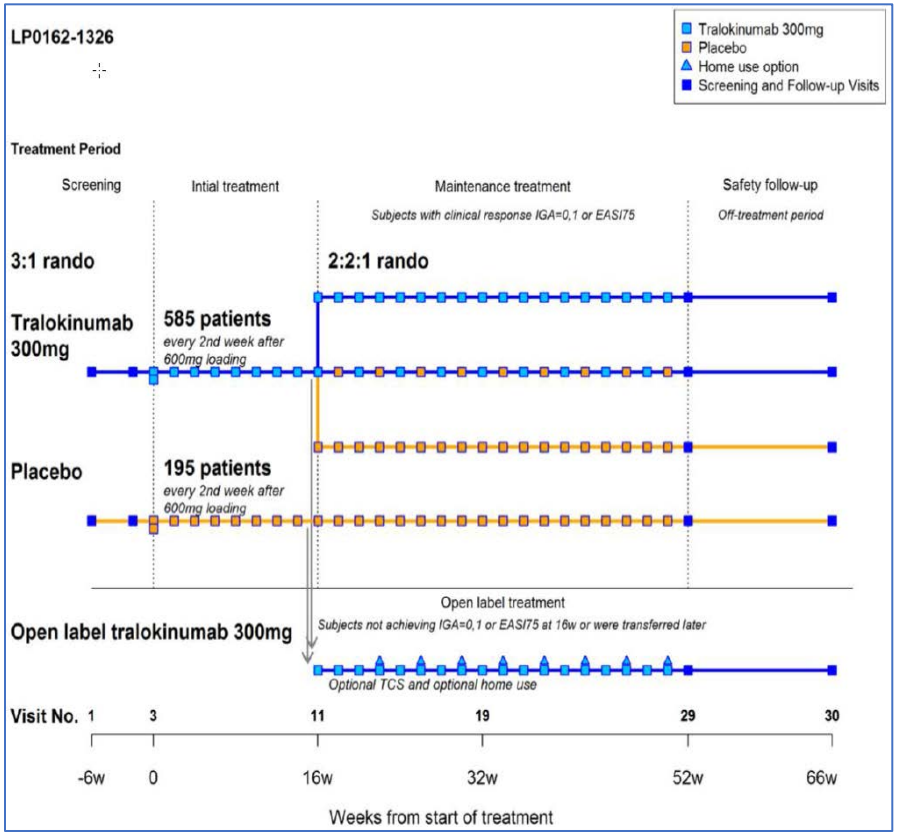
**Figure 7. Trial Design Schematic for the Monotherapy Trials—ECZTRA-1 and ECZTRA-2**

**ECZTRA-1**



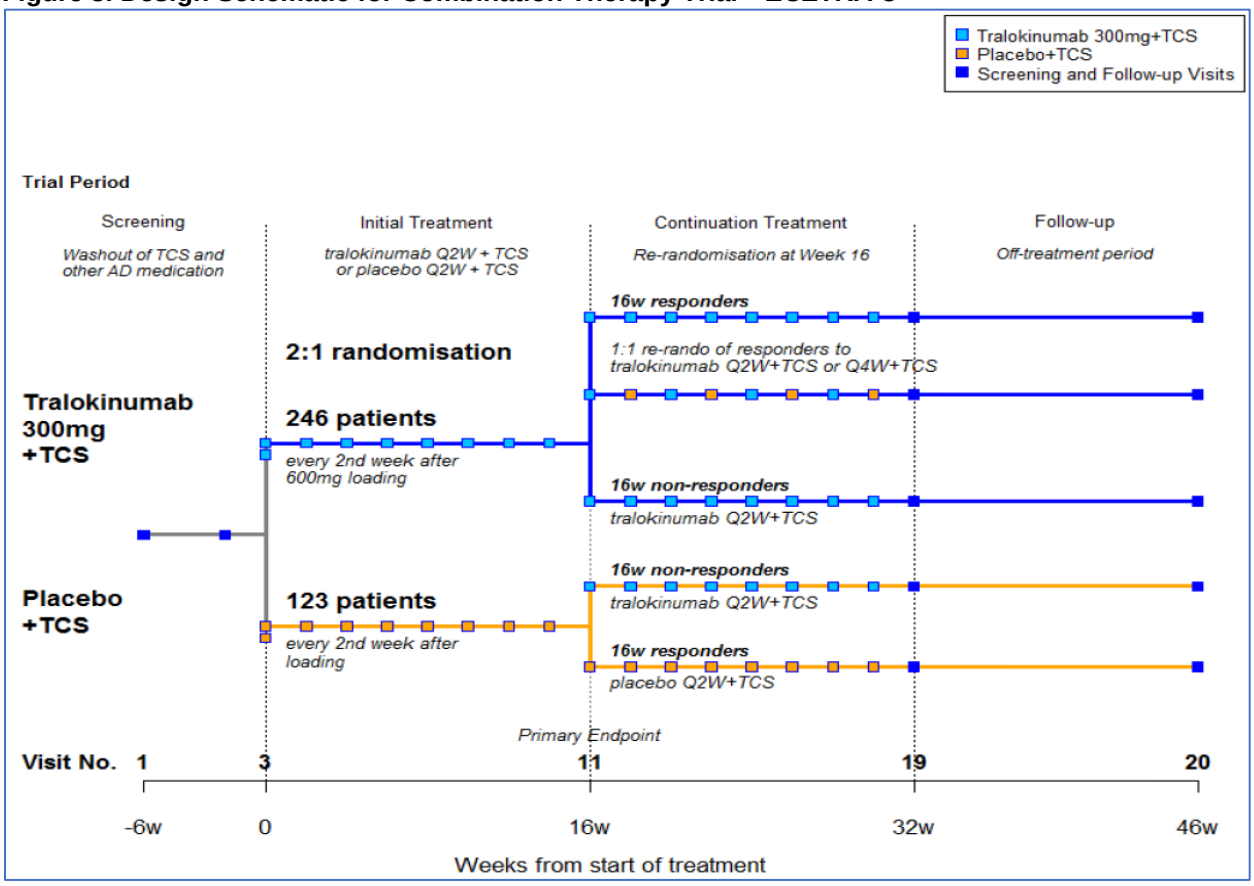

Source: Applicant's Clinical Study Report for ECZTRA-1.
Abbreviations: EASI-75, at least 75% reduction in Eczema Area and Severity Index score; ECZTRA, ECZema TRAlokinumab; IGA, Investigator's Global Assessment; no., number; rando, randomization; TCS, topical corticosteroid; w, week

**ECZTRA-2**




Source: Applicant's Clinical Study Report for ECZTRA-2.
Abbreviations: EASI-75, at least 75% reduction in Eczema Area and Severity Index score; ECZTRA, ECZema TRAlokinumab; IGA, Investigator's Global Assessment; no., number; rando, randomization; TCS, topical corticosteroid; w, week

**Figure 8. Design Schematic for Combination Therapy Trial—ECZTRA-3**




Source: Applicant's Clinical Study Report for ECZTRA-3.
Abbreviations: AD, atopic dermatitis; EASI, Eczema Area and Severity Index; EASI-75, at least 75% reduction in EASI score; ECZTRA, ECZema TRAlokinumab; IGA, Investigator's Global Assessment; no., number; Q2W, every 2 weeks; Q4W, every 4 weeks; rando, randomization; TCS, topical corticosteroid; w, week

### 6.2.2. Eligibility Criteria

The following were the key inclusion criteria for all three Phase 3 trials:

(1) Male or female 18 years or older.
(2) Diagnosis of AD as defined by established criteria (Hanifin 1980).
(3) Diagnosis of AD for at least 1 year.
(4) AD involvement of ≥10% of body surface area at screening and baseline.
(5) An Investigator's Global Assessment (IGA) score of ≥3 at screening and at baseline; see Table 8 for details on the IGA scale.
(6) An EASI score of ≥12 at screening and 16 at baseline; see Table 9 for details on the calculation of EASI.
(7) A Worst Daily Pruritus NRS average score of ≥4 during the week prior to baseline.
(8) Applied a stable dose of emollient twice daily (or more, as needed) for at least 14 days before randomization.
(9) Have a recent history (within 1 year before the screening visit) of inadequate response to treatment with topical medications or for whom topical treatments are otherwise medically inadvisable (e.g., due to important side effects or safety risks).

**Table 8. Investigator's Global Assessment (IGA) Scale**

| Score | Disease severity | Standard IGA scale | IGA morphological descriptors |
|---|---|---|---|
| 0 | Clear | No inflammatory signs of atopic dermatitis | No erythema and no elevation (papulation/infiltration). |
| 1 | Almost clear | Just perceptible erythema, and just perceptible papulation/infiltration | Barely perceptible erythema and/or minimal lesion elevation (papulation/infiltration) that is not widespread. |
| 2 | Mild disease | Mild erythema and mild papulation/infiltration | Visibly detectable, light pink erythema and very slight elevation (papulation/infiltration). |
| 3 | Moderate disease | Moderate erythema and moderate papulation/infiltration | Dull red, clearly distinguishable erythema and clearly perceptible but not extensive elevation (papulation/infiltration). |
| 4 | Severe disease | Severe erythema and severe papulation/infiltration | Deep/dark red erythema, marked and extensive elevation (papulation/infiltration). |

Source: Applicant's Clinical Study Reports for ECZTRA-1/ECZTRA-2.

**Table 9. Eczema Area and Severity Index (EASI)**

| Body region | Erythema | Induration/ papulation | Excoriation | Lichenification | Area score | Weighting factor | Score |
|---|---|---|---|---|---|---|---|
| **Head/neck** | ( SS + | SS + | SS + | SS ) | x AS | x 0.1 | |
| **Trunk** | ( SS + | SS + | SS + | SS ) | x AS | x 0.3 | |
| **Upper extremities** | ( SS + | SS + | SS + | SS ) | x AS | x 0.2 | |
| **Lower extremities** | ( SS + | SS + | SS + | SS ) | x AS | x 0.4 | |
| **The EASI score is the sum of the 4 body region scores** | | | | | | | (range 0-72) |

| Severity score scale | |
|---|---|
| 0 | None/absent |
| 1 | Mild |
| 2 | Moderate |
| 3 | Severe |

Half-points (0.5; 1.5; 2.5) could also be used.

| Area score scale | |
|---|---|
| 0 | 0% affected area |
| 1 | 1% to 9% affected area |
| 2 | 10% to 29% affected area |
| 3 | 30% to 49% affected area |
| 4 | 50% to 69% affected area |
| 5 | 70% to 89% affected area |
| 6 | 90% to 100% affected area |

Source: Applicant's Clinical Study Reports for ECZTRA-1/ECZTRA-2.
Abbreviations: AS, area score; SS, severity score

## Worst Daily Pruritus Numeric Rating Scale

Subjects assessed their worst itch severity over the past 24 hr using an 11-point NRS (Worst Daily Pruritus NRS) with 0 indicating *no itch* and 10 indicating *worst itch imaginable*. Subjects completed the Worst Daily Pruritus NRS as part of an eDiary each day in the morning from Week -2 (visit 2) until Week 52 (Week 32 for ECZTRA-3).

### 6.2.3. Endpoints

For all three Phase 3 trials, the protocols specified the following primary efficacy endpoints:

- Proportion of subjects with an IGA score of 0 (clear) or 1 (almost clear) (IGA 0/1) at Week 16.
- Proportion of subjects with at least a 75% reduction in EASI score from baseline (EASI-75) to Week 16.

The Agency noted in the advice letter dated 6/23/2017 that because IGA 0/1 and EASI-75 at Week 16 are sequentially tested in the order listed above, the IGA 0/1 is considered to be the primary endpoint and EASI-75 is considered a key secondary endpoint.

The protocols/Statistical Analysis Plans (SAPs) specified the following secondary efficacy endpoints:

- Reduction of Worst Daily Pruritus NRS score (weekly average) ≥4 from baseline to Week 16; the weekly average Worst Daily Pruritus NRS score was calculated only if at least four daily assessments were available.
- Change in SCORAD from baseline to Week 16.
- Change in DLQI score from baseline to Week 16.

The protocols/SAPs also specified the following secondary maintenance endpoints:

- Monotherapy trials, ECZTRA-1 and ECZTRA-2:
  - IGA 0/1 at Week 52 among subjects with an IGA score of 0/1 at Week 16 after initial randomization to tralokinumab.
  - EASI-75 at Week 52 among subjects with EASI-75 at Week 16 after initial randomization to tralokinumab.
- Trial ECZTRA-3:
  - IGA 0/1 at Week 32 among subjects with an IGA of 0/1 at Week 16 after initial randomization to tralokinumab.
  - EASI-75 at Week 32 among subjects with EASI-75 at Week 16 after initial randomization to tralokinumab.

During the Pre-BLA meeting (meeting minutes dated 5/10/2019), the Applicant acknowledged the Agency's comments that formal testing during the maintenance period and testing for the DLQI and SCORAD endpoints are not required because findings from these tests will not be included in labeling. The Applicant clarified that such endpoints are intended for scientific publication. Therefore, endpoints based on DLQI and SCORAD are not presented in this review, and secondary maintenance endpoints are considered exploratory.

The protocols also specified *additional secondary endpoints* and *other endpoints* and *other maintenance endpoints*. However, such endpoints are not included in the multiplicity testing strategy, and therefore, are not presented in this review.

## 6.2.4. Statistical Analysis Plan

### Analysis Populations

The primary analysis population specified in the SAPs is the full analysis set, defined as all randomized subjects who were exposed to the investigational medicinal product (IMP).

The protocols/SAPs also specified supportive analyses using the per-protocol set, defined to exclude subjects from the full analysis set for whom any of the following conditions apply:

- Receive no treatment with the IMP.
- Provide no efficacy data following start of treatment.
- Are known to have taken the wrong IMP throughout the initial treatment period of the trial.
- Do not fulfill the disease-defining inclusion criteria (#2, #4 to #6 in Section 6.2.2).

A maintenance analysis set (referred to as continuation treatment analysis set for ECZTRA-3) was defined in the protocols as all subjects who receive tralokinumab in the initial treatment period and who are rerandomized to maintenance/continuation treatment. Subjects who were not exposed to maintenance/continuation treatment were excluded from the maintenance/ continuation treatment analysis set, according to the SAPs.

**Estimands**

The following three estimands were defined in the protocols/SAPs for the analysis of the primary and binary secondary endpoints. These estimands incorporated two main types of intercurrent events that influenced how the treatment effects were estimated: initiation of rescue medication and permanent discontinuation of IMP.

- Primary estimand, *composite*: Treatment difference in response rates of IGA 0/1 and EASI-75 after 16 weeks achieved without rescue medication, regardless of treatment discontinuation.
- Secondary estimand, *hypothetical*: Treatment difference in response rates of IGA 0/1 and EASI-75 after 16 weeks if all subjects adhered to the treatment regimen in the sense that they did not discontinue IMP permanently and no rescue medication was made available before Week 16.
- Tertiary estimand, *treatment policy*: Treatment difference in response rate after 16 weeks regardless of rescue medication and treatment discontinuation.

**Analysis Methods for the Primary and Binary Secondary Endpoints**

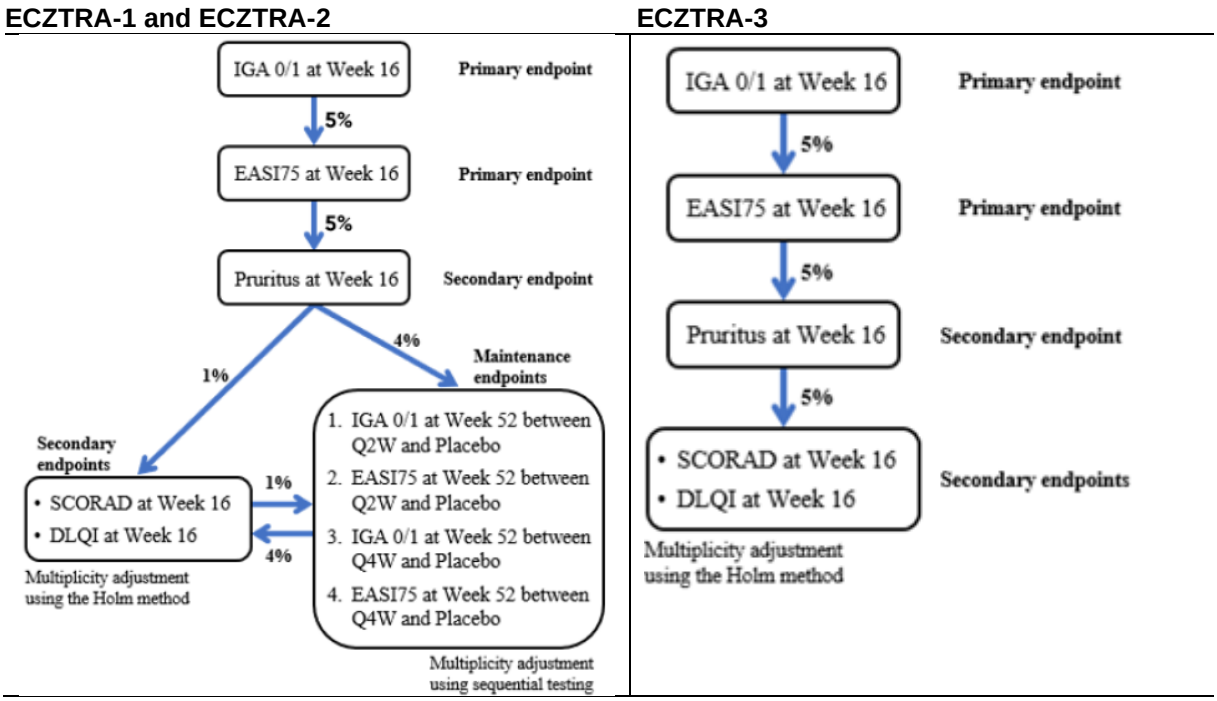
The protocols/SAPs specified analyzing the primary endpoints (i.e., IGA 0/1 and EASI-75) and the binary secondary endpoint based on Worst Daily Pruritus NRS using the Cochran–Mantel–Haenszel test stratified by region (ECZTRA-1: North America, Europe, and Japan; ECZTRA-2: North America, Europe, Australia, and Asia) and disease severity (baseline IGA of 3 or 4). Analyses for the primary and tertiary estimands used the full analysis set. For the analysis of the secondary estimand, the Applicant stated that “data collected after permanent discontinuation of IMP or after initiation of rescue medication are not applied in the analysis.”

The analysis of the primary estimand was repeated based on the per protocol analysis set. According to the SAPs, the weekly average of Worst Daily Pruritus NRS was calculated only if at least four assessments were available.

## Multiplicity Adjustment Strategy

The overall type-1 error rate was controlled for the primary analyses of the primary estimands for the primary and secondary endpoints for the initial and maintenance treatment periods using the testing procedure outlined in Figure 9.

**Figure 9. Testing Procedure (United States Submission)**




Source: Applicant's Statistical Analysis Plans for ECZTRA-1, ECZTRA-2, and ECZTRA-3.
Arrows indicate order of testing when superiority is shown for all endpoints within a box.
Abbreviations: DLQI, Dermatology Life Quality Index; EASI-75, at least 75% reduction in Eczema Area and Severity Index score; IGA, Investigator's Global Assessment; Q2W, every 2 weeks; Q4W, every 4 weeks; SCORAD, scoring atopic dermatitis

## Analysis Methods for the Maintenance Endpoints (Monotherapy Trials ECZTRA-1 and 2)

For the two dichotomous maintenance endpoints, IGA 0/1 and EASI-75 at Week 52, an adapted version of the primary estimand (composite estimand) for the primary endpoints was considered:

- Treatment difference in response rates of IGA 0/1 and EASI-75 after 52 weeks achieved without rescue medication and without transfer to open-label treatment.

The adapted estimand takes into account that subjects were actively discontinued from the treatment randomized at Week 16 throughout the maintenance period and transferred to the open-label tralokinumab arm if they met the prespecified treatment failure criteria described in Section III.15.

**Methods for Handling the Missing Data**

Table 10 summarizes the protocol/SAP-specified methods for handling missing data in the analysis of the primary and binary secondary endpoints.

**Table 10. Methods for Handling the Missing Data for the Primary and Binary Secondary Endpoints**

| Estimand | Primary Analysis | Sensitivity Analyses |
|---|---|---|
| Primary estimand, composite | NRI (subjects who received rescue medication prior to Week 16 and subjects who did not attend the Week 16 visit but did not receive rescue medication prior to Week 16 were considered nonresponders) | Sensitivity analysis 1: All subjects who have permanently discontinued IMP prior to Week 16 were imputed as nonresponders, even if no rescue medication had been used. |
| | | Sensitivity analysis 2: Same as primary analysis, with the exception that missing data at Week 16 was imputed using LOCF rather than nonresponder imputation for subjects who did not receive rescue medication and did not withdraw due to an AE or lack of efficacy. |
| | | Sensitivity analysis 3: A tipping point analysis using MI:<br>Subjects who, prior to the Week 16 visit, had received rescue medication were considered nonresponders. Missing Week 16 response was imputed from a Bernoulli distribution with varying parameter p for subjects in the placebo group who did not use rescue medication. Subjects in the tralokinumab group with missing Week 16 data were imputed as nonresponders. Different percentages of placebo subjects were considered responders for the different values of p. The tipping point is the value of p that changed the conclusion from significant to nonsignificant.<br>The MI procedure included the following steps for each value of *p*=100 copies of the dataset will be generated (seed=11109925) and missing Week 16 data imputed for subjects in the placebo arm from a Bernoulli distribution with parameter *p*. |
| Secondary estimand, hypothetical | IGA 0/1: MI of the underlying 5-point IGA values, using an ordinal logistic regression model with the effects of region, and baseline disease severity (IGA 3 or 4) as factors (100 datasets; seed=11109925). In each group, intermittent missing values were imputed using LOCF to obtain a monotone missing data pattern.<br>EASI-75 and pruritus NRS: MI of the underlying EASI/NRS values, using an ANCOVA model with the effects of baseline value as a covariate, and region and baseline disease severity (IGA 3 or 4) as factors (100 datasets; seed=11109925). Intermittent missing values were imputed in each group using the MCMC method (100 datasets; seed=290997). | MI of missing data at Week 16 using a pattern mixture model, where missing data in the tralokinumab arm as well as the placebo arm will be imputed from observed data in the placebo arm ("using a so-called copy-reference approach"). The protocols stated that "with this exemption, the stepwise multiple imputation procedure and subsequent analysis will be conducted in the same way as specified for the primary analysis of the secondary estimand." |
| Tertiary estimand, treatment policy | MI within four groups, defined according to randomized treatment arm and whether subjects have permanently discontinued IMP prior to Week 16. | NRI |

Source: Statistical Reviewer's table; excerpts from the Applicant's protocols and statistical analysis plans.
Abbreviations: AE, adverse event; ANCOVA, analysis of covariance; EASI-75, at least 75% reduction in Eczema Area and Severity Index score; IGA, Investigator's Global Assessment; IMP, investigational medicinal product; LOCF, last observation carried forward; MI, multiple imputation; MCMC, Markov chain Monte Carlo; NRI, nonresponder imputation; NRS, numeric rating scale

For the primary analysis of the maintenance endpoints in the monotherapy trials (ECZTRA-1 and -2), all subjects who, prior to Week 52, received rescue medication, and/or were transferred to the open-label arm, were considered nonresponders. In addition, all subjects with missing maintenance endpoint data at the Week 52 visit were also imputed as nonresponders. In a sensitivity analysis, data missing at Week 52 for subjects who did not receive rescue medication, did not transfer to open-label, and did not withdraw from the trial due to an adverse event (AE) or lack of efficacy were imputed using last observation carried forward.

### 6.2.5. Results of Analyses

This section summarizes subject disposition, baseline demographics, and disease characteristics, followed by primary and secondary efficacy results to support the efficacy of tralokinumab in adult subjects with moderate-to-severe AD.

Due to several concerns about good clinical practices (GCP) noncompliance and data integrity, the review team decided to exclude Sites 423, 435 (ECZTRA-2), and 818 (ECZTRA-3) from the evaluations of safety and efficacy. More information regarding the removal of these sites from the safety and efficacy evaluations is provided in Section III.16. The review team otherwise concluded that the conduct of the trials appears to be adequate and the data generated appears to be acceptable to support the use of this product for the proposed indication.

#### Subject Disposition, Demographics, and Baseline Disease Characteristics

Trial ECZTRA-1 enrolled and randomized a total of 802 subjects; however, 2 subjects in each arm were not dosed. Trial ECZTRA-2 enrolled and randomized a total of 772 subjects; however, 2 subjects in the tralokinumab Q2W arm were not dosed. Trial ECZTRA-3 enrolled and randomized (and also dosed) a total of 368 subjects. The reasons for subjects not being dosed include major protocol deviations, meeting exclusion criteria, withdrawing consent, and refusing injection.

Table 11 presents the disposition of subjects during the initial treatment period (first 16 weeks) of ECZTRA-1, ECZTRA-2, and ECZTRA-3. The discontinuation rates were generally similar across the treatment arms within each trial; except for ECZTRA-2, in which the discontinuation rate was slightly higher in the placebo arm.

**Table 11. Subject Disposition to Week 16—ECZTRA-1, ECZTRA-2, and ECZTRA-3 (FAS[1])**

| | ECZTRA-1 | | ECZTRA-2 | | ECZTRA-3 | |
|---|---|---|---|---|---|---|
| Parameter | Tralokinumab Q2W N=601 n (%) | Placebo N=197 n (%) | Tralokinumab Q2W N=577 n (%) | Placebo N=193 n (%) | Tralokinumab Q2W+TCS N=243 n (%) | Placebo +TCS N=123 n (%) |
| Discontinued before Week 16 | 51 (8) | 18 (9) | 32 (6) | 20 (11) | 17 (7) | 6 (5) |
| Adverse event | 12 (2) | 6 (3) | 7 (1) | 4 (2) | 5 (2) | 1 (1) |
| Lost to follow-up | 11 (2) | 2 (1) | 3 (<1) | 1 (<1) | 4 (2) | 0 (0) |
| Withdrawal by subject | 9 (1) | 6 (3) | 9 (2) | 4 (2) | 6 (2) | 1 (1) |
| Lack of efficacy | 6 (1) | 2 (1) | 5 (1) | 4 (2) | 1 (<1) | 1 (1) |
| Other | 13 (2) | 2 (1) | 8 (1) | 7 (4) | 1 (<1) | 3 (2) |
| Completed Week 16 on treatment[2] | 550 (91) | 179 (90) | 545 (94) | 173 (89) | 226 (93) | 117 (95) |
| Assigned to maintenance treatment | 185 (31) | 29 (15) | 219 (38) | 27 (14) | 224 (92) | 117 (95) |
| Transferred to open-label treatment | 360 (60) | 146 (73) | 323 (56) | 144 (74) | N/A | N/A |
| Discontinued at Week 16 | 11 (2) | 4 (2) | 6 (1) | 2 (1) | 2 (1) | 0 (0) |

Source: Statistical Reviewer's analysis; Sites 423, 435 (ECZTRA-2) and 818 (ECZTRA-3) were removed.
[1] FAS was defined as all randomized subjects who were dosed.
[2] No permanent discontinuation of IMP before Week 16.
Abbreviations: ECZTRA, ECZema TRAlokinumab; FAS, full analysis set; N/A, not applicable; Q2W, every 2 weeks; TCS, topical corticosteroids

Demographics for the three trials are presented in Table 12. Demographics were generally balanced across the treatment arms within each trial. However, in ECZTRA-3, a slightly larger proportion of males was randomized to the placebo arm compared to the tralokinumab arm, and a larger proportion of white subjects was randomized to the tralokinumab arm compared to the placebo arm. The demographics were similar across the three trials. The majority of the subjects were male (approximately 60%) and white (approximately 70%). The mean age was approximately 38 years.

Table 13 presents the baseline disease characteristics for all trials. The baseline disease characteristics were generally balanced across the treatment arms. In general, approximately equal proportions of subjects with an IGA score of 3 (moderate) and an IGA score of 4 (severe) were enrolled in the three trials.

**Table 12. Demographics—Trials ECZTRA-1, ECZTRA-2, and ECZTRA-3 (FAS[1])**

| | ECZTRA-1 | | ECZTRA-2 | | ECZTRA-3 | |
|---|---|---|---|---|---|---|
| **Parameter** | **Tralokinumab Q2W (N=601)** | **Placebo (N=197)** | **Tralokinumab Q2W (N=577)** | **Placebo (N=193)** | **Tralokinumab Q2W+TCS N=243** | **Placebo +TCS N=123** |
| Sex, n (%) | | | | | | |
| Male | 350 (58%) | 122 (62%) | 347 (60%) | 108 (56%) | 120 (49%) | 83 (67%) |
| Female | 251 (42%) | 75 (38%) | 230 (40%) | 85 (44%) | 123 (51%) | 40 (33%) |
| Age, years | | | | | | |
| Mean (standard deviation) | 38.6 (13.7) | 39.3 (15.3) | 36.9 (14.7) | 34.8 (14.0) | 39.1 (14.7) | 37.5 (14.8) |
| Median | 37 | 36 | 34 | 29 | 37 | 34 |
| Range | 18-92 | 18-82 | 18-86 | 18-80 | 18-79 | 18-78 |
| Age group (years), n (%) | | | | | | |
| 18-64 | 572 (95%) | 183 (93%) | 548 (95%) | 186 (96%) | 231 (95%) | 115 (94%) |
| 65-84 | 28 (5%) | 14 (7%) | 28 (5%) | 7 (4%) | 12 (5%) | 8 (6%) |
| ≥85 | 1 (<1%) | 0 (0%) | 1 (<1%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Race[2], n (%) | | | | | | |
| White | 424 (71%) | 137 (70%) | 370 (64%) | 123 (64%) | 194 (80%) | 81 (66%) |
| Black or African American | 41 (7%) | 17 (9%) | 31 (5%) | 9 (5%) | 22 (9%) | 12 (10%) |
| American Indian or Alaska Native | 1 (<1%) | 0 (0%) | 2 (<1%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Native Hawaiian or other Pacific Islander | 5 (1%) | 0 (0%) | 1 (<1%) | 0 (0%) | 1 (<1%) | 1 (1%) |
| Asian | 120 (20%) | 40 (20%) | 154 (26%) | 52 926%) | 17 (7%) | 24 (19%) |
| Other | 8 (1%) | 0 (0%) | 19 (3%) | 9 (5%) | 9 (4%) | 5 (4%) |

| Parameter | ECZTRA-1 Tralokinumab Q2W (N=601) | ECZTRA-1 Placebo (N=197) | ECZTRA-2 Tralokinumab Q2W (N=577) | ECZTRA-2 Placebo (N=193) | ECZTRA-3 Tralokinumab Q2W+TCS N=243 | ECZTRA-3 Placebo +TCS N=123 |
|---|---|---|---|---|---|---|
| Country, n (%) | | | | | | |
| United States | 149 (25%) | 48 (24%) | 110 (19%) | 39 (20%) | 62 (25%) | 25 (20%) |
| Germany | 199 (33%) | 72 (36%) | - | - | 42 (17%) | 15 (12%) |
| France | 84 (14%) | 23 (12%) | - | - | - | - |
| Spain | 73 (12%) | 23 (12%) | - | - | 12 (5%) | 15 (12%) |
| Japan | 96 (16%) | 31 (16%) | - | - | - | - |
| Canada | - | - | 146 (25%) | 44 (23%) | 34 (14%) | 26 (21%) |
| Australia | - | - | 90 (15%) | 31 (15%) | | |
| Great Britain | - | - | 53 (9%) | 15 (8%) | 21 (9%) | 13 (11%) |
| Denmark | - | - | 8 (1%) | 2 (1%) | - | - |
| Italy | - | - | 31 (5%) | 10 (5%) | - | - |
| Poland | - | - | 67 (12%) | 27 (14%) | 48 (20%) | 19 (15%) |
| Russia | - | - | 14 (2%) | 5 (3%) | - | - |
| Korea | - | - | 58 (10%) | 20 (10%) | - | - |
| Belgium | - | - | - | - | 15 (6%) | 4 (3%) |
| The Netherlands | - | - | - | - | 9 (4%) | 6 (5%) |

Source: Statistical Reviewer's analysis; Sites 423, 435 (ECZTRA-2), and 818 (ECZTRA-3) were removed.
[1] FAS was defined as all randomized subjects who were dosed.
[2] Missing race information for five subjects in Trial ECZTRA-1: two in the tralokinumab Q2W arm and two in the placebo arm.
Abbreviations: ECZTRA, ECZema TRAlokinumab; FAS, full analysis set; Q2W, every 2 weeks; TCS, topical corticosteroids

**Table 13. Baseline Disease Characteristics—ECZTRA-1, ECZTRA-2, and ECZTRA-3 (FAS[1])**

| | ECZTRA-1 | | ECZTRA-2 | | ECZTRA-3 | |
|---|---|---|---|---|---|---|
| Characteristic | Tralokinumab Q2W (N=601) | Placebo (N=197) | Tralokinumab Q2W (N=577) | Placebo (N=193) | Tralokinumab Q2W+TCS (N=243) | Placebo +TCS (N=123) |
| IGA Score | | | | | | |
| 3, Moderate | 296 (49%) | 95 (48%) | 296 (51%) | 93 (48%) | 127 (52%) | 64 (52%) |
| 4, Severe | 305 (51%) | 102 (52%) | 281 (49%) | 100 (51%) | 116 (48%) | 59 (48%) |
| EASI Score | | | | | | |
| Mean (SD) | 32.2 (13.7) | 32.9 (13.9) | 32.4 (14.3) | 33.1 (13.8) | 29.1 (12.0) | 30.4 (12.9) |
| Median | 28.2 | 30.3 | 28.6 | 30.8 | 25.4 | 26.2 |
| Range | 16-72 | 16-70.8 | 15.4-72 | 16-72 | 15.8-68.4 | 16.1-72 |
| Pruritus NRS | | | | | | |
| Mean (SD) | 7.7 (1.4) | 7.7 (1.4) | 7.9 (1.5) | 8.0 (1.3) | 7.7 (1.5) | 7.9 (1.5) |
| Median | 7.9 | 7.9 | 8 | 8.1 | 8 | 8 |
| Range | 2.5-10 | 3-10 | 2.3-10 | 4-10 | 3-10 | 4.4-10 |
| ≥3 | 597 (99%) | 195 (99%) | 570 (99%) | 192 (99%) | 242 (100%) | 126 (100%) |
| ≥4 | 594 (99%) | 194 (98%) | 563 (98%) | 192 (99%) | 240 (99%) | 123 (100%) |
| BSA | | | | | | |
| Mean (SD) | 52.7 (24.1) | 54.4 (25.5) | 53.2 (25.4) | 54.3 (24.6) | 47.9 (23.6) | 49.1 (26.1) |
| Median | 50 | 53 | 50 | 50 | 42 | 40 |
| Range | 10-100 | 10-100 | 10-100 | 11-100 | 11-100 | 12-100 |

Source: Statistical Reviewer's analysis; Sites 423, 435 (ECZTRA-2), and 818 (ECZTRA-3) were removed.
[1] FAS was defined as all randomized subjects who were dosed.
Abbreviations: BSA, body surface area; EASI, Eczema Area and Severity Index; ECZTRA, ECZema TRAlokinumab; FAS, full analysis set; IGA, Investigator's Global Assessment; NRS, numeric rating scale; Q2W, every 2 weeks; SD, standard deviation; TCS, topical corticosteroids

## Use of Rescue Medication

The use of rescue medication is summarized by treatment arm in Table 14 for the initial treatment period. The use of rescue medication during the maintenance period is summarized in Table 15 for the monotherapy trials (ECZTRA-1 and ECZTRA-2) and in Table 16 for the combination therapy trial (ECZTRA-3).

In the initial treatment period, a higher proportion of subjects used rescue medication in the placebo arm compared to the tralokinumab arm in the three pivotal trials. The proportion of subjects who used rescue medication was slightly higher in ECZTRA-1 compared to ECZTRA-2 in both treatment arms. As expected, a much smaller proportion of subjects used rescue medication in the combination therapy trial. Note that these subjects were considered as nonresponders for the efficacy analyses at Week 16.

In the maintenance period, a higher proportion of subjects used rescue medication in the placebo arm compared to the tralokinumab arm in the monotherapy trials. In the combination therapy trial, all subjects in the tralokinumab Q2W arm who used rescue medication were nonresponders at Week 16.

**Table 14. Rescue Medication During Initial Treatment Period—ECZTRA-1, ECZTRA-2, and ECZTRA-3 (FAS[1])**

| | ECZTRA-1 | | ECZTRA-2 | | ECZTRA-3 | |
|---|---|---|---|---|---|---|
| Medication | Tralokinumab Q2W (N=601) | Placebo (N=197) | Tralokinumab Q2W (N=577) | Placebo (N=193) | Tralokinumab Q2W+TCS (N=243) | Placebo +TCS (N=123) |
| Any rescue medication | 216 (36%) | 92 (47%) | 135 (23%) | 89 (46%) | 7 (3%) | 13 (11%) |

Source: Statistical Reviewer's analysis; Sites 423, 435 (ECZTRA-2), and 818 (ECZTRA-3) were removed.
[1] FAS was defined as all randomized subjects who were dosed.
Subjects from Site 818 were excluded from ECZTRA-3.
Abbreviations: ECZTRA, ECZema TRAlokinumab; FAS, full analysis set; Q2W, every 2 weeks; TCS, topical corticosteroids

**Table 15. Rescue Medication During Maintenance Period—ECZTRA-1 and ECZTRA-2 (MAS[1])**

| | ECZTRA-1 | | | ECZTRA-2 | | |
|---|---|---|---|---|---|---|
| | Tralokinumab | | | Tralokinumab | | |
| Medication | Q2W (N=68) | Q4W (N=76) | Placebo (N=35) | Q2W (N=90) | Q4W (N=84) | Placebo (N=44) |
| Any rescue medication | 20 (29%) | 26 (34%) | 15 (43%) | 17 (19%) | 20 (24%) | 9 (20%) |

Source: Statistical Reviewer's analysis; Sites 423, 435 (ECZTRA-2) and 818 (ECZTRA-3) were removed.
[1] MAS was defined as all subjects who received tralokinumab in the initial treatment period and who were rerandomized to maintenance treatment. Subjects not exposed to maintenance treatment were excluded from the MAS.
Abbreviations: ECZTRA, ECZema TRAlokinumab; MAS, maintenance analysis set; Q2W, every 2 weeks; Q4W, every 4 weeks

**Table 16. Rescue Medication During Continuation Period—ECZTRA-3 (Continuation Treatment Analysis Set[1])**

| Medication | Tralokinumab Q2W+TCS (N=234) | Tralokinumab Q4W+TCS (N=66) | Placebo+TCS (N=41) |
|---|---|---|---|
| Any rescue medication | 15 (6%) | 1 (1%) | 1 (2%) |

Source: Statistical Reviewer's analysis; Sites 423, 435 (ECZTRA-2), and 818 (ECZTRA-3) were removed.
[1] Continuation treatment analysis set was defined as all subjects who received tralokinumab in the initial treatment period and who were rerandomized to continuation treatment. Subjects who were not exposed to continuation treatment were excluded.
Abbreviations: ECZTRA, ECZema TRAlokinumab; Q2W, every 2 weeks; Q4W, every 4 weeks; TCS, topical corticosteroids

## Results for the Primary and Secondary Efficacy Endpoints During the Initial Treatment Period

Table 17 presents the results for the primary and secondary efficacy endpoints at Week 16 for ECZTRA-1 and ECZTRA-2. Table 18 lists the results for the primary and secondary efficacy endpoints at Week 16 for ECZTRA-3. Tralokinumab was statistically superior to placebo for the primary endpoint of IGA success (defined as scoring 0 or 1) at Week 16, as well as for the secondary endpoints of EASI-75 and pruritus NRS (i.e., at least 4-point reduction from baseline in Worst Daily Pruritus NRS score) at Week 16 in the three trials. Of note, a greater treatment effect was observed in ECZTRA-2 compared to ECZTRA-1 for all endpoints. The results in the per-protocol population (not shown herein) were similar to those in the intent-to-treat population.

The results in Table 17 and Table 18 do not include Sites 423, 435 (ECZTRA-2), and 818 (ECZTRA-3), as described above. However, the results with these sites included were similar to those in Table 17 and Table 18 (see Table 68 and Table 69 in Section III.16).

The statistical reviewer also summarized the results for the endpoint of EASI-90 at Week 16, defined as at least 90% reduction from baseline, which are supportive of the results for primary and secondary endpoints. EASI-90 was prespecified as an *additional secondary endpoint* and was not included in the multiple testing procedure. Therefore, the results for such endpoint are viewed as exploratory for this review (refer to Table 74 and Table 75 in Section III.16).

**Table 17. Results for the Primary and Secondary Endpoints at Week 16—ECZTRA-1 and ECZTRA-2 (FAS; Primary Analysis; Primary Estimand[1])**

| | ECZTRA-1 | | ECZTRA-2 | |
|---|---|---|---|---|
| Endpoint | Tralokinumab Q2W (N=601) | Placebo (N=197) | Tralokinumab Q2W (N=577) | Placebo (N=193) |
| IGA 0/1 (Primary) | 95 (16%) | 14 (7%) | 123 (21%) | 18 (9%) |
| Difference (95% CI) | 9% (4%, 13%) | | 12% (7%, 17%) | |
| P-Value | 0.0017 | | <0.001 | |
| EASI-75 | 150 (25%) | 25 (13%) | 188 (33%) | 19 (10%) |
| Difference (95% CI) | 12% (7%, 18%) | | 22% (17%, 28%) | |
| P-Value | <0.001 | | <0.001 | |
| Worst Daily Pruritus NRS[2] | 119/594 (20%) | 20/194 (10%) | 141/563 (25%) | 17/192 (9%) |
| Difference (95% CI) | 10% (4%, 15%) | | 16% (11%, 21%) | |
| P-Value | 0.002 | | <0.001 | |

Source: Statistical Reviewer's analysis (same as Applicant's analysis except for ECZTRA-2, which excluded Sites 423 and 435, and ECZTRA-3, which excluded Site 818 in the above table).
[1] FAS was defined as all randomized subjects who were dosed: Subjects who received rescue medication considered nonresponders; subjects with missing data at Week 16 imputed as nonresponders.
[2] Reduction of Worst Daily Pruritus NRS score (weekly average) ≥4 from baseline to Week 16, among subjects with a baseline score of ≥4.
Difference, 95% CI, and p-value are based on the Cochran–Mantel–Haenszel test stratified by region and baseline IGA score.
Abbreviations: CI, confidence interval; EASI-75, at least 75% reduction in Eczema Area and Severity Index score; FAS, full analysis set; IGA, Investigator's Global Assessment; NRS, numeric rating scale; Q2W, every 2 weeks

**Table 18. Results for the Primary and Secondary Endpoints at Week 16—ECZTRA-3 (FAS; Primary Analysis; Primary Estimand[1])**

| Endpoint | Tralokinumab Q2W+TCS (N=243) | Placebo +TCS (N=123) |
|---|---|---|
| IGA 0/1 (Primary) | 92 (38%) | 33 (27%) |
| Difference (95% CI) | 11% (1%, 21%) | |
| P-Value | 0.033 | |
| EASI-75 | 136 (56%) | 45 (37%) |
| Difference (95% CI) | 20% (9%, 30%) | |
| P-Value | <0.001 | |
| Worst Daily Pruritus NRS[2] | 111/240 (46%) | 43/123 (35%) |
| Difference (95% CI) | 11% (1%, 22%) | |
| P-Value | 0.040 | |

Source: Statistical Reviewer's analysis (same as Applicant's analysis, except for Trial ECZTRA-2, which excluded Sites 423 and 435, and Trial ECZTRA-3, which excluded Site 818 in the above table).
[1] FAS was defined as all randomized subjects who were dosed: Subjects who received rescue medication considered nonresponders; subjects with missing data at Week 16 imputed as nonresponders.
[2] Reduction of Worst Daily Pruritus NRS score (weekly average) ≥4 from baseline to Week 16, among subjects with baseline score of ≥4.
Difference, 95% CI, and p-value are based on the Cochran–Mantel–Haenszel test stratified by region and baseline IGA score.
Abbreviations: CI, confidence interval; EASI-75, at least 75% reduction in Eczema Area and Severity Index score; FAS, full analysis set; IGA, Investigator's Global Assessment; NRS, numeric rating scale; Q2W, every 2 weeks; TCS, topical corticosteroids

Overall, the proportion of subjects with missing data was relatively small. In ECZTRA-2, the proportion of subjects with missing data at Week 16 (i.e., primary timepoint) was slightly larger in the placebo arm compared to the tralokinumab arm; whereas in ECZTRA-3, the proportion of subjects with missing data at Week 16 was slightly smaller in the placebo arm compared to the tralokinumab arm. The proportion of subjects with missing data for Week 16 was slightly smaller in ECZTRA-3 compared to ECZTRA-1 and ECZTRA-2 (see Table 70 in Section III.16). Table 71 to Table 73 in Section III.16 present the results for the primary and secondary efficacy endpoints in all three pivotal trials by the various imputation methods for each estimand. The

results for all endpoints in consideration were similar across the primary analysis and the sensitivity analyses for each estimand. For a detailed discussion of the results refer to Section III.16.

Based on the Applicant's tipping-point analysis for the primary estimand, the result was no longer statistically significant when assuming a placebo IGA 0/1 response in subjects without rescue medication and with missing data at Week 16 of 99% in ECZTRA-1 and 71% in ECZTRA-2. The tipping point was not met for IGA 0/1 in ECZTRA-3. The tipping point was not met in for EASI-75 response in all three trials. Furthermore, the result was no longer statistically significant when assuming a placebo worst pruritus NRS response in subjects without rescue medication and with missing data at Week 16 of 42% in ECZTRA-1, 99.9% in ECZTRA-2, and >8% in ECZTRA-3.

Refer to Section III.16 for plots of the efficacy over time during the initial treatment period.

## Results for the Secondary Efficacy Endpoints During the Maintenance Period

### Monotherapy Trials (ECZTRA-1 and ECZTRA-2)

Week 16 tralokinumab responders were rerandomized in a 2:2:1 ratio to tralokinumab 300 mg Q2W, tralokinumab 300 mg Q4W, or placebo maintenance regimens. Response was defined as IGA of 0/1 or EASI-75. Randomization was stratified by region and IGA response at Week 16 (IGA 0/1 or IGA >1). Week 16 placebo responders continued to receive placebo Q2W in the maintenance treatment period. For the disposition of subjects during the maintenance period see Table 76 in Section III.16.

Among the 218 subjects in the maintenance analysis set, defined as all subjects who received tralokinumab in the initial treatment period and who were rerandomized to (and dosed with) a maintenance regimen, 123 subjects were IGA 0/1 responders and 185 were EASI-75 responders at Week 16 without receiving rescue medication during the initial treatment period. Table 19 presents the proportions of subjects who maintained IGA 0/1 and EASI-75 responses at Week 52. During the Pre-BLA meeting on 05/01/2019, the Agency noted that formal statistical testing against subjects rerandomized to placebo for maintenance is not meaningful, and therefore, maintenance endpoints are considered exploratory. In ECZTRA-1, the proportion of subjects who maintained their response (IGA 0/1 and EASI-75) was smaller in the tralokinumab Q4W arm compared to the tralokinumab Q2W arm. In ECZTRA-2, the proportion of subjects who maintained their response (IGA 0/1 and EASI-75) was comparable across the two tralokinumab arms. In both trials, the proportion of subjects who maintained their response (IGA 0/1 and EASI-75) was larger in the tralokinumab arms compared to the placebo arms.

**Table 19. Proportion of Subjects who Maintained their Response at Week 52—ECZTRA-1 and ECZTRA-2 (Composite Estimand; MAS; NRI[1])**

| | ECZTRA-1 | | | ECZTRA-2 | | |
|---|---|---|---|---|---|---|
| Parameter | Tralokinumab Q2W n (%) | Tralokinumab Q4W n (%) | Placebo n (%) | Tralokinumab Q2W n (%) | Tralokinumab Q4W n (%) | Placebo n (%) |
| IGA 0/1 at Week 52 | N=39<br>20 (51) | N=36<br>14 (39) | N=19<br>9 (47) | N=53<br>32 (60) | N=44<br>22 (50) | N=26<br>6 (23) |
| EASI-75 at Week 52 | N=47<br>28 (60) | N=57<br>28 (49) | N=30<br>10 (33) | N=76<br>43 (57) | N=69<br>38 (55) | N=40<br>8 (20) |

Source: Statistical Reviewer's analysis; Sites 423 and 435 from ECZTRA-2 were removed.
[1] MAS was defined as all subjects who received tralokinumab in the initial treatment period and who were rerandomized to maintenance treatment; subjects who were not exposed to maintenance treatment were excluded. Subjects who received rescue medication or were transferred to open-label treatment were considered nonresponders. Missing data at Week 52 were imputed using the nonresponder imputation method.
Abbreviations: EASI-75, at least 75% reduction in Eczema Area and Severity Index score; ECZTRA, ECZema TRAlokinumab; IGA, Investigator's Global Assessment; MAS, maintenance analysis set; Q2W, every 2 weeks; Q4W, every 4 weeks

The maintenance of response in ECZTRA-1 was similar across the active doses and placebo, which was not the case in ECZTRA-2. This was also observed in the plots of efficacy over time during the maintenance period, which are presented in Section III.16. We note that such results are in line with those of the initial treatment period, where the treatment effect in ECZTRA-2 was slightly greater than that in ECZTRA-1. In addition, the maintenance results in ECZTRA-1 could be attributed to the generally small treatment effect and the small number of subjects treated with placebo during the maintenance period.

The median time-to-loss of IGA 0/1 response was 10 weeks in the tralokinumab Q2W arm, 7.7 weeks in the tralokinumab Q4W arm, and 7.7 weeks in the placebo arm for ECZTRA-1. For ECZTRA-2, the median time-to-loss of IGA 0/1 response was 19.6 weeks in the tralokinumab Q2W arm, 18 weeks in the tralokinumab Q4W arm, and 5.5 weeks in the placebo arm.

The median time-to-loss of EASI-75 response was not reached in the tralokinumab Q2W arm, was 18 weeks in the tralokinumab Q4W arm, and 16 weeks in the placebo arm for ECZTRA-1. For ECZTRA-2, the median time-to-loss of EASI-75 response was 37.6 weeks in the tralokinumab Q2W arm, 23.6 weeks in the tralokinumab Q4W arm, and 12 weeks in the placebo arm.

We note that the time-to-loss of response is defined as the time from rerandomization at Week 16 until the first occurrence of IGA>1 (according to IGA 0/1) and not achieving EASI-75, initiation of rescue mediation, or transfer to open-label, whichever came first, among Week 16 responders without rescue medication after initial randomization to tralokinumab.

## Trial ECZTRA-3 (Adjunct to TCS)

Week 16 tralokinumab+TCS responders were rerandomized in a 1:1 ratio to tralokinumab 300 mg Q2W+TCS or tralokinumab 300 mg Q4W+TCS (continuation regimens). Again, response was defined as IGA of 0 or 1 or EASI-75, and randomization was stratified by region and IGA response at Week 16 (IGA 0/1 or IGA >1). Week 16 placebo responders continued to receive placebo Q2W in the continuation treatment period. For the disposition of subjects during the continuation treatment period see Table 77 in Section III.16.

Among the 131 subjects in the continuation treatment analysis set, 91 subjects were IGA 0/1 responders and 127 subjects were EASI-75 responders at Week 16 without receiving rescue

medication during the initial treatment period. Table 20 presents the proportion of subjects who maintained their IGA 0/1 and EASI-75 responses at Week 32. The proportion of subjects who maintained their responses (IGA 0/1 and EASI-75) was smaller in the tralokinumab Q4W arm compared to the tralokinumab Q2W arm.

**Table 20. Proportion of Subjects Who Maintained a Response at Week 32—ECZTRA-3 (Composite Estimand; Continuation Treatment Analysis Set; NRI[1])**

| Parameter | Tralokinumab Q2W+TCS n (%) | Tralokinumab Q4W+TCS n (%) |
|---|---|---|
| IGA 0/1 at Week 32 | 40/45 (89) | 35/46 (76) |
| EASI-75 at Week 32 | 60/65 (92) | 56/62 (90) |

Source: Statistical Reviewer's analysis; Site 818 was removed.
[1] Continuation treatment analysis set was defined as all randomized subjects who did not withdraw from the trial before or at the Week 16 visit and who were exposed to at least one dose of the investigational medicinal product in the continuation treatment period. Subjects who received rescue medication were considered nonresponders. Missing data at Week 32 were imputed using the nonresponder imputation method.
Abbreviations: EASI-75, at least 75% reduction in Eczema Area and Severity Index score; ECZTRA, ECZema TRAlokinumab; IGA, Investigator's Global Assessment; Q2W, every 2 weeks; Q4W, every 4 weeks

For IGA 0/1 responders at Week 16 who were rerandomized to continuation treatment period, the median time-to-loss of IGA 0/1 was not reached in the tralokinumab Q2W+TCS arm, and was 11 weeks in the tralokinumab+TCS Q4W arm.

For EASI-75 responders at Week 16 who were rerandomized to maintenance treatment, the median time-to-loss of EASI-75 was not reached in either the tralokinumab Q2W+TCS arm or the tralokinumab+TCS Q4W arm.

Refer to Section III.16 for plots of efficacy over time during the maintenance period.

## Subgroup Analyses

Results for subgroups analyses by age (18 to 64 and ≥65 years), sex, race (white, nonwhite), body weight (<70, 70 to 100, >100 kg), baseline IGA score, and prior use of immunosuppressants are presented in Table 78 to Table 83 in Section III.16.

The sample size in the subgroups of subjects ≥65 years of age and subjects of body weight >100 kg was very small; therefore, it would be difficult to detect any differences in efficacy between these subgroups and their complements. For race, the treatment effect for both IGA0/1 and EASI-75 was lower in nonwhite subjects in ECZTRA-1 but higher in nonwhite subjects in ECZTRA-3. However, the sample size of nonwhite subjects was too small in ECZTRA-3 to allow conclusions. In ECZTRA-2, the treatment effect was comparable across white and nonwhite subjects. For body weight, the treatment effect for IGA0/1 was slightly lower in subjects with a body weight of 70 to 100 kg compared to those of body weight <70 kg in the monotherapy trials.

The treatment effect was generally consistent across the baseline IGA score subgroups and with prior use of immunosuppressants. In ECZTRA-3, a smaller treatment effect was observed in subjects with a baseline IGA score of 3 (moderate); however, this was due to a larger placebo+TCS response in this subgroup compared to subjects with a severe baseline IGA score.

ECZTRA-1 was conducted in five countries (Germany, Japan, France, Spain, and the United States), ECZTRA-2 was conducted in nine countries (Canada, Australia, Poland, Republic of

Korea, Great Britain, Italy, Russia, Denmark, and the United States), and ECZTRA-3 was conducted in eight countries (i.e., Poland, Canada, Germany, Great Britain, Spain, Belgium, The Netherlands, and the United States). Table 84 to Table 86 in Section III.16 present the efficacy results for IGA 0/1 and EASI-75 at Week 16 by country. In all three trials, there was some variability in treatment effect across the countries; however, this may be due to the relatively small sample sizes in several of the countries.

# 7. Risk and Risk Management

The overall assessment of safety of tralokinumab is informed by a variety of sources, including nonclinical toxicology, safety pharmacology studies, and early phase clinical studies. The safety assessment for the intended population of AD subjects is based primarily on the Phase 3 trials.

After completing the interdisciplinary analysis and review, the team resolved any risk issues and identified none that might impact approval of the application. Due to the limited information regarding pregnancy impacts, pregnancy registries will be recommended as postmarketing requirements.

## 7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

The nonclinical safety profile of tralokinumab supporting this BLA has been adequately evaluated in (1) in vitro and in vivo pharmacology studies, (2) repeat-dose toxicity studies in cynomolgus monkeys (up to 6 months), including safety pharmacology assessment, (3) reproductive and developmental toxicity studies in cynomolgus monkeys, including two fertility, one pilot embryo-fetal development, one prenatal and one postnatal development studies, and an enhanced prenatal and postnatal development (ePPND) study, (4) a tissue cross-reactivity study in human tissues, and (5) a carcinogenicity risk assessment for tralokinumab. Genotoxicity and carcinogenicity studies were not conducted because they are not considered applicable and/or warranted. PK/ toxicokinetics were studied as part of the toxicity studies and in a separate animal PK study in cynomolgus monkeys.

The target organs of toxicity or off-target tissue binding of the mAb were not identified. Systemic pharmacologic effects did not suggest a potential risk to humans. There were no nonclinical safety issues of significant concern as assessed by the nonclinical studies conducted during the development program. (b) (4) (tralokinumab) is approvable for the treatment of moderate-to-severe AD in adults from a Pharmacology/Toxicology perspective.

Refer to Section III.13 for details.

## 7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

As with all therapeutic proteins, there is a potential for immunogenicity with tralokinumab. However, no clinically meaningful differences in the PK, safety, or efficacy of tralokinumab-ldrm were observed in patients who tested positive for anti-tralokinumab-ldrm antibody (including neutralizing antibodies).

Hypersensitivity reactions, including anaphylaxis and angioedema, have been reported with use of tralokinumab.

## 7.3. Potential Safety Concerns Identified Through Postmarket Experience

There is no postmarketing experience to date with tralokinumab. Clinical trial safety experience is described in Section 7.4.

## 7.4. FDA Approach to the Safety Review

The Applicant submitted safety data from five clinical trials for tralokinumab in patients with moderate-to-severe AD:

- Two 52-week monotherapy trials (ECZTRA-1 and ECZTRA-2).
- One 32-week combination therapy (tralokinumab+TCS) trial (ECZTRA-3).
- One 16-week vaccine response trial (ECZTRA-5).
- One 12-week Phase 2b dose-finding trial (D2213C00001).

The main safety data pools, as described in the integrated summary of safety (ISS)-SAP include the following:

- Monotherapy pool (ECZTRA-1, -2) for initial and maintenance/open-label periods up to 52 weeks (pooling is appropriate because of identical protocols and randomization ratios).
- AD pool (ECZTRA-1, -2, -3, and -5, and the 300 mg dose group of the Phase 2b trial) is the primary pool for evaluation of safety for initial treatment and safety follow-up periods. Adjusted weights are used to mitigate the effects of different randomization ratios across trials and to avoid Simpson's paradox.
- Exposure pool includes all clinical trials with tralokinumab in AD, asthma, ulcerative colitis, and idiopathic pulmonary fibrosis.

The monotherapy and the AD pools were used for the evaluation of treatment-emergent adverse events (TEAEs), adverse events of special interest (AESIs), laboratory results, vital signs, and electrocardiogram (ECG) results. In addition, the monotherapy pool was used for subgroup analyses of safety data. The exposure pool was used to evaluate overall exposure, deaths, pregnancies, rare events, and major adverse cardiovascular events.

AEs were coded by Medical Dictionary for Regulatory Activities (MedDRA) (v. 20.0) for all ECZTRA trials and recoded from MedDRA (v. 17.1) to MedDRA (v. 20.0) for Phase 2b trial D2213C00001 for inclusion in the AD pool.

The JumpStart team of the Office of Computational Science conducted a preliminary review of the safety data, including ISS Overview Assessment (5/27/2020), Study Data Tabulation Model to Analysis Data Model Traceability Assessment (5/28/2020), and Core Data Fitness Report (5/11/2020). Additional data fitness assessments were conducted by the clinical data safety team for this BLA.

No major data quality or integrity issues were identified that would preclude performing a safety review for this BLA. There were no major issues identified with respect to recording, coding, and categorizing AEs. The Applicant's translations of verbatim terms to MedDRA PTs for the events reported in ECZTRA-1, -2, and -3 were reviewed and found to be acceptable.

TEAEs were protocol-defined as "any untoward medical occurrence in a patient or clinical investigation subject administered tralokinumab and which does not necessarily have a causal relationship with this treatment." All AEs in the reviewed trials were classified by severity (mild, moderate, or severe), causality (*probably related*, *possibly related*, or *not related*), and outcome (recovered/ resolved, recovering/ resolving, not recovered/ not resolved, recovered/ resolved with sequelae, fatal, and unknown), which was reviewed and found to be acceptable.

An SAE was defined as any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/ incapacity, a congenital anomaly/ birth defect, or is a medically important condition (e.g., events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition of SAE).

AESIs were predefined in the trial protocols based on the potential and established areas of safety interest for monoclonal antibodies in the treatment of AD, including eczema herpeticum, malignancies diagnosed after randomization (excluding basal cell carcinoma, localized squamous cell carcinoma of the skin, and carcinoma in situ of the cervix), skin infections requiring systemic treatment, and eye disorders (conjunctivitis, keratoconjunctivitis, and keratitis).

Other safety areas of interest for tralokinumab are infections (severe or serious infections, infections requiring treatment with parenteral antibiotics or treatment exceeding 2 weeks with oral antibiotics/antivirals/antifungal drugs, opportunistic infections [OIs; including clinical endoparasitosis or tuberculosis]), anaphylaxis and serious allergic reactions, immune complex disease, injection site reactions, medication errors, suicidality and psychiatric disorders, cardiovascular (CV) events of interest, and rare events.

Laboratory parameters were classified as low, normal, or high, depending on their value relative to their reference range, with shift tables to compare their values at the end of treatment with their baseline values. Any laboratory abnormality assessed as clinically significant by the Investigator was recorded as an AE.

## 7.5. Adequacy of Clinical Safety Database

The safety database is adequate for comprehensive safety assessment of tralokinumab for the proposed indication, patient population, dosage regimen, and duration. The number of subjects exposed and duration of exposure are adequate to satisfy the recommendations of the International Council on Harmonisation (ICH) E1A guidelines.

In the AD pool of five completed AD trials (ECZTRA-1, -2, -3, -5 and Phase 2b), 1991 subjects were exposed to tralokinumab. In the Phase 3 efficacy and safety trials ECZTRA-1, ECZTRA-2, and ECZTRA-3; a total of 1446 subjects received at least one dose of tralokinumab, 1188 subjects were treated with tralokinumab for at least 16 weeks, and 807 subjects in the monotherapy group were treated with tralokinumab for 52 weeks.

**Table 21. Duration of Exposure, Safety Population, Initial Treatment Period (Weeks 0 to 16)—ECZTRA-1, ECZTRA-2, and ECZTRA-3**

| Variable | ECZTRA-1+2 Tralokinumab N=1194 n (%) | ECZTRA-1+2 Placebo N=396 n (%) | ECZTRA-3 Tralokinumab N=252 n (%) | ECZTRA-3 Placebo N=126 n (%) |
|---|---|---|---|---|
| Duration of treatment (weeks) | | | | |
| Mean (SD) | 15.6 (2.6) | 15.2 (3.5) | 15.7 (2.5) | 15.8 (1.9) |
| Median (minimum, maximum) | 16.1 (0.1, 24.3) | 16.1 (0.1, 25.4) | 16.1 (0.1, 19.0) | 16.1 (5.1, 17.3) |
| Subjects treated, by duration, n (%) | | | | |
| <6 weeks | 29 (2.4) | 20 (5.1) | 6 (2.4) | 1 (0.8) |
| ≥6 to <12 weeks | 37 (3.1) | 15 (3.8) | 7 (2.8) | 4 (3.2) |
| ≥12 to <16 weeks | 152 (12.7) | 50 (12.6) | 27 (10.7) | 8 (6.3) |
| ≥16 weeks | 976 (81.7) | 311 (78.5) | 212 (84.1) | 113 (89.7) |

Source: Clinical data safety reviewer for BLA 761180, adex.xpt; software: Python.
Abbreviations: ECZTRA, ECZema TRAlokinumab; N, number of subjects in group; n, number of subjects with given treatment duration; SD, standard deviation

**Table 22. Duration of Exposure, Safety Population, Maintenance Period—ECZTRA-1, ECZTRA-2 (Weeks 16 to 52), and ECZTRA-3 (Weeks 16 to 32)**

| Variable | ECZTRA-1+2 Tralokinumab Q2W N=159 n (%) | ECZTRA-1+2 Tralokinumab Q4W N=165 n (%) | ECZTRA-1+2 Placebo N=141 n (%) | ECZTRA-3 Tralokinumab Q2W N=243 n (%) | ECZTRA-3 Tralokinumab Q4W N=69 n (%) | ECZTRA-3 Placebo N=41 n (%) |
|---|---|---|---|---|---|---|
| Duration of treatment (weeks) | | | | | | |
| Mean (SD) | 27.9 (12.1) | 27.8 (11.8) | 25.0 (12.5) | 15.7 (2.1) | 15.7 (2.2) | 15.6 (2.4) |
| Median (minimum, maximum) | 36.0 (0.1, 38.1) | 36.0 (2.1, 38.1) | 30.3 (1.4, 39.0) | 16.1 (3.9, 19.3) | 16.1 (4.1, 18.1) | 16.1 (1.9, 17.4) |
| Subjects treated, by duration, n (%) | | | | | | |
| <12 weeks | 28 (17.6) | 28 (17.0) | 30 (21.3) | 10 (4.1) | 3 (4.3) | 2 (4.9) |
| ≥12 to <24 weeks | 18 (11.3) | 24 (14.5) | 29 (20.6) | 233 (95.9) | 66 (95.7) | 39 (95.1) |
| ≥24 to <36 weeks | 31 (19.5) | 25 (15.2) | 21 (14.9) | 0 | 0 | 0 |
| ≥36 to <48 weeks | 82 (51.6) | 88 (53.3) | 61 (43.3) | 0 | 0 | 0 |
| ≥48 weeks | 0 | 0 | 0 | 0 | 0 | 0 |

Source: Clinical data safety reviewer for BLA 761180, adex.xpt; software: Python.
Abbreviations: ECZTRA, ECZema TRAlokinumab; N, number of subjects in group; n, number of subjects with given treatment duration; Q2W, every 2 weeks; Q4W, every 4 weeks; SD, standard deviation

**Table 23. Duration of Exposure, Safety Population—ECZTRA-1 and ECZTRA-2 (Open-Label Period (Weeks 16 to 52)**

| Variable | ECZTRA-1 Tralokinumab Q2W+ Optional TCS N=563 n (%) | ECZTRA-2 Tralokinumab Q2W+ Optional TCS N=558 n (%) | ECZTRA-1+2 Tralokinumab Q2W+ Optional TCS N=1121 n (%) |
|---|---|---|---|
| Duration of treatment (weeks) | | | |
| Mean (SD) | 32.4 (12.2) | 29.6 (10.3) | 31.0 (11.4) |
| Median (min, max) | 36.1 (0.1, 53.1) | 36.0 (0.1, 42.4) | 36.0 (0.1, 53.1) |
| Subjects treated, by duration, n (%) | | | |
| <12 weeks | 55 (9.8) | 52 (9.3) | 107 (9.5) |
| ≥12 to <24 weeks | 60 (10.7) | 91 (16.3) | 151 (13.5) |
| ≥24 to <36 weeks | 106 (18.8) | 123 (22.0) | 229 (20.4) |
| ≥36 to <48 weeks | 278 (49.4) | 292 (52.3) | 570 (50.8) |
| ≥48 weeks | 64 (11.4) | 0 | 64 (5.7) |

Source: Clinical data safety reviewer for BLA 761180, adex.xpt; software: Python.
Abbreviations: ECZTRA, ECZema TRAlokinumab; max, maximum; min, minimum; N, number of subjects in group; n, number of subjects with given treatment duration; Q2W, every 2 weeks; SD, standard deviation; TCS, topical corticosteroids

# 7.6. Safety Findings and Concerns Based on Review of Clinical Safety Database

The Applicant provided an adequate assessment of the safety profile of tralokinumab 300 mg, administered SC biweekly, for the treatment of adult subjects with moderate-to-severe AD. Safety data were submitted for two Phase 2 trials (dose-finding study D2213C00001 and vaccine trial ECZTRA-5) and three Phase 3 trials (ECZTRA-1, ECZTRA-2, and ECZTRA-3) of tralokinumab. The Phase 3 safety data are discussed below.

## 7.6.1. Safety Findings and Concerns, Trials ECZTRA-1, ECZTRA-2, and ECZTRA-3

### Overall Treatment-Emergent Adverse Event Summary

Table 24 to Table 26 provide overviews of the TEAEs reported for the initial treatment period (Weeks 0 to 16), maintenance treatment period (Weeks 16 to ≤52) for the monotherapy pool (ECZTRA-1, -2) or (Weeks 16 to ≤32) for ECZTRA-3, and the open-label period for the monotherapy pool.

During the initial treatment period, the overall incidence, severity, and actions taken in response to the TEAEs were well balanced between the active treatment and placebo groups.

During the maintenance treatment period, TEAEs were more frequent and more severe in the tralokinumab Q2W group compared to tralokinumab Q4W or placebo group, and more frequent actions were taken in response to TEAEs in the tralokinumab Q2W group compared to the Q4W group.

**Table 24. Overview of Adverse Events, Safety Population, Trials ECZTRA-1 and ECZTRA-2, and ECZTRA-3 (Initial Treatment Period)**

| Event Category | ECZTRA-1+2 Tralokinumab N=1194 n (%) | ECZTRA-1+2 Placebo N=396 n (%) | Risk Difference (95% CI)1 | ECZTRA-3 Tralokinumab N=252 n (%) | ECZTRA-3 Placebo N=126 n (%) |
|---|---|---|---|---|---|
| Any AE | 824 (69.0) | 283 (71.5) | -2.5 (-7.7, 2.7) | 180 (71.4) | 84 (66.7) |
| Any treatment-related AE | 337 (28.2) | 119 (30.1) | -1.9 (-7.1, 3.3) | 108 (42.9) | 34 (27.0) |
| Moderate or severe AE | 431 (36.1) | 193 (48.7) | -12.6 (-18.2, -7.0) | 69 (27.4) | 33 (26.2) |
| Any SAE | 33 (2.8) | 13 (3.3) | -0.5 (-2.5, 1.5) | 2 (0.8) | 4 (3.2) |
| SAE with fatal outcome | 0 | 0 | 0.0 (0.0, 0.0) | 0 | 0 |
| AE leading to discontinuation of study drug | 29 (2.4) | 11 (2.8) | -0.4 (-2.2, 1.4) | 6 (2.4) | 1 (0.8) |
| AE leading to dose modification of study drug | 44 (3.7) | 30 (7.6) | -3.9 (-6.7, -1.1) | 7 (2.8) | 3 (2.4) |
| AE leading to interruption of study drug | 43 (3.6) | 30 (7.6) | -4.0 (-6.8, -1.2) | 7 (2.8) | 3 (2.4) |
| AE leading to reduction of study drug | 1 (0.1) | 0 | 0.1 (-0.1, 0.3) | 0 | 0 |
| AE leading to delay of study drug | 0 | 0 | 0.0 (0.0, 0.0) | 0 | 0 |

Source: Clinical data safety reviewer for BLA 761180, adae.xpt; software: Python.
Treatment-emergent adverse events defined as events starting after first use of the investigational medicinal product.
[1] Risk difference column shows absolute difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: AE, adverse event; CI, confidence interval; ECZTRA, ECZema TRAlokinumab; N, number of subjects in group; n, number of subjects with at least one event; SAE, serious adverse event

**Table 25. Overview of Adverse Events, Safety Population, Trials ECZTRA-1, ECZTRA-2, and ECZTRA-3 (Maintenance Period)**

| Event Category | ECZTRA-1+2 Tralokinumab Q2W N=159 n (%) | ECZTRA-1+2 Tralokinumab Q4W N=165 n (%) | ECZTRA-1+2 Placebo N=141 n (%) | ECZTRA-3 Tralokinumab Q2W N=243 n (%) | ECZTRA-3 Tralokinumab Q4W N=69 n (%) | ECZTRA-3 Placebo N=41 n (%) |
|---|---|---|---|---|---|---|
| Any AE | 116 (73.0) | 109 (66.1) | 91 (64.5) | 165 (67.9) | 41 (59.4) | 26 (63.4) |
| Moderate or severe AE | 62 (39.0) | 47 (28.5) | 44 (31.2) | 74 (30.5) | 12 (17.4) | 12 (29.3) |
| Any SAE | 1 (0.6) | 6 (3.6) | 1 (0.7) | 5 (2.1) | 0 | 1 (2.4) |
| SAE with fatal outcome | 0 | 0 | 0 | 0 | 0 | 0 |
| AE leading to discontinuation of study drug | 3 (1.9) | 2 (1.2) | 0 | 3 (1.2) | 1 (1.4) | 1 (2.4) |
| AE leading to dose modification of study drug | 8 (5.0) | 4 (2.4) | 8 (5.7) | 10 (4.1) | 0 | 4 (9.8) |
| AE leading to interruption of study drug | 8 (5.0) | 4 (2.4) | 8 (5.7) | 10 (4.1) | 0 | 4 (9.8) |
| AE leading to reduction of study drug | 0 | 0 | 0 | 0 | 0 | 0 |
| AE leading to delay of study drug | 0 | 0 | 0 | 0 | 0 | 0 |

Source: Clinical data safety reviewer for BLA 761180, adae.xpt; software: Python.
Treatment-emergent adverse events defined as events starting after first use of the investigational medicinal product.
Abbreviations: AE, adverse event; ECZTRA, ECZema TRAlokinumab; N, number of subjects in treatment arm; n, number of subjects with at least one event; Q2W, every 2 weeks; Q4W, every 4 weeks; SAE, serious adverse event

**Table 26. Overview of Adverse Events, Safety Population, Trials ECZTRA-1 and ECZTRA-2 (Open-Label Period)**

| Event Category | ECZTRA-1 Tralokinumab Q2W+Optional TCS N=563 n (%) | ECZTRA-2 Tralokinumab Q2W+Optional TCS N=558 n (%) | ECZTRA-1+2 Tralokinumab Q2W+Optional TCS N=1121 n (%) |
|---|---|---|---|
| Any AE | 435 (77.3) | 379 (67.9) | 814 (72.6) |
| Moderate or severe AE | 232 (41.2) | 210 (37.6) | 442 (39.4) |
| Any SAE | 27 (4.8) | 16 (2.9) | 43 (3.8) |
| SAE with fatal outcome | 0 | 0 | 0 |
| AE leading to discontinuation of study drug | 17 (3.0) | 11 (2.0) | 28 (2.5) |
| AE leading to dose modification of study drug | 23 (4.1) | 32 (5.7) | 55 (4.9) |
| AE leading to interruption of study drug | 23 (4.1) | 32 (5.7) | 55 (4.9) |
| AE leading to reduction of study drug | 0 | 0 | 0 |
| AE leading to delay of study drug | 0 | 0 | 0 |

Source: Clinical data safety reviewer for BLA 761180, adae.xpt; software: Python
Treatment-emergent adverse events defined as an event starting after the first use of IMP (investigational medicinal product).
Abbreviations: AE, adverse event; ECZTRA, ECZema TRAlokinumab; N, number of subjects in treatment arm; n, number of subjects with at least one event; Q2W, every 2 weeks; SAE, serious adverse event; TCS, topical corticosteroids

## Deaths, AD Pool

No deaths were reported during the initial treatment, maintenance, or open-label treatment periods in trials ECZTRA-1, ECZTRA-2, or ECZTRA-3. Two deaths were reported during Phase 2 trials (D2213C00001 and ECZTRA-5), and three deaths were reported after completion of Trials ECZTRA-1 and ECZTRA-2. Refer to Section III.17 for narratives of deaths.

## Serious Adverse Events, ECZTRA-1, ECZTRA-2, and ECZTRA-3

### Initial Treatment Period

During the initial treatment period for the monotherapy trials (ECZTRA-1, ECZTRA-2) and tralokinumab+TCS (ECZTRA-3) trial, SAEs were reported less frequently in the tralokinumab groups than the placebo groups (Table 27).

SAEs occurred at a rate of <1% for all SOCs in the tralokinumab and placebo groups, with the highest risk differences in the pooled monotherapy trials for the SOCs of injury, poisoning, and procedural complications (0.3%), and neoplasms benign, malignant, and unspecified (including cysts and polyps), 0.2%). For all other SOCs, the risk difference was ≤0.1% (one subject). For ECZTRA-3, two SAEs were reported at 0.4% (one subject) for the SOCs of immune system disorders and gastrointestinal disorders in the tralokinumab+TCS group, compared to 0 in the placebo group. SAEs reported by Narrow FDA Medical Query in at least one subject in the pooled monotherapy trials included malignancy and bronchospasm (two subjects each).

Refer to the SAE narratives for subjects in the tralokinumab treatment groups during the initial treatment period in Section III.17. Most SAEs were assessed by the Investigators/Applicant as *not related*. The following SAEs were assessed by the Investigators as *possibly related* or *probably related*:

- ECZTRA-1: Eosinophilia - Subject (b) (6), Hyperhidrosis - Subject: (b) (6), Injection site reaction - Subject: (b) (6) Leishmaniasis - Subject: (b) (6) Dermatitis exfoliative generalized - Subject: (b) (6), Asthma - Subject: (b) (6)
- ECZTRA-2: Pneumonia - Subject: (b) (6)

**Table 27. Serious Adverse Events, Safety Population, ECZTRA-1+2, ECZTRA-3 (Initial Treatment Period)**

| Preferred Term | ECZTRA-1+2 Tralokinumab N=1194 n (%) | ECZTRA-1+2 Placebo N=396 n (%) | Risk Difference (95% CI)1 | ECZTRA-3 Tralokinumab N=252 n (%) | ECZTRA-3 Placebo N=126 n (%) |
|---|---|---|---|---|---|
| Any SAE | 33 (2.8) | 13 (3.3) | -0.5 (-2.5, 1.5) | 2 (0.8) | 4 (3.2) |
| Dermatitis atopic | 5 (0.4) | 1 (0.3) | 0.1 (-0.5, 0.7) | 0 | 0 |
| Accessory cardiac pathway | 1 (0.1) | 0 | 0.1 (-0.1, 0.3) | 0 | 0 |
| Acute left ventricular failure | 1 (0.1) | 0 | 0.1 (-0.1, 0.3) | 0 | 0 |
| Alcohol poisoning | 1 (0.1) | 0 | 0.1 (-0.1, 0.3) | 0 | 0 |
| Angiosarcoma | 1 (0.1) | 0 | 0.1 (-0.1, 0.3) | 0 | 0 |
| Atrial fibrillation | 1 (0.1) | 0 | 0.1 (-0.1, 0.3) | 0 | 0 |
| Cellulitis | 1 (0.1) | 0 | 0.1 (-0.1, 0.3) | 0 | 0 |
| Depression suicidal | 1 (0.1) | 0 | 0.1 (-0.1, 0.3) | 0 | 0 |
| Duodenal ulcer | 1 (0.1) | 0 | 0.1 (-0.1, 0.3) | 0 | 0 |
| Eosinophilia | 1 (0.1) | 0 | 0.1 (-0.1, 0.3) | 0 | 0 |
| Gastroenteritis viral | 1 (0.1) | 0 | 0.1 (-0.1, 0.3) | 0 | 0 |
| Hyperhidrosis | 1 (0.1) | 0 | 0.1 (-0.1, 0.3) | 0 | 0 |
| Hypertensive encephalopathy | 1 (0.1) | 0 | 0.1 (-0.1, 0.3) | 0 | 0 |
| Incarcerated umbilical hernia | 1 (0.1) | 0 | 0.1 (-0.1, 0.3) | 0 | 0 |
| Injection site reaction | 1 (0.1) | 0 | 0.1 (-0.1, 0.3) | 0 | 0 |
| Intentional overdose | 1 (0.1) | 0 | 0.1 (-0.1, 0.3) | 0 | 0 |
| Leishmaniasis | 1 (0.1) | 0 | 0.1 (-0.1, 0.3) | 0 | 0 |
| Multiple fractures | 1 (0.1) | 0 | 0.1 (-0.1, 0.3) | 0 | 0 |
| Peripheral artery stenosis | 1 (0.1) | 0 | 0.1 (-0.1, 0.3) | 0 | 0 |
| Pneumonia | 1 (0.1) | 0 | 0.1 (-0.1, 0.3) | 0 | 0 |
| Pneumothorax spontaneous | 1 (0.1) | 0 | 0.1 (-0.1, 0.3) | 0 | 0 |
| Pulmonary embolism | 1 (0.1) | 0 | 0.1 (-0.1, 0.3) | 0 | 0 |
| Squamous cell carcinoma of skin | 1 (0.1) | 0 | 0.1 (-0.1, 0.3) | 0 | 0 |
| Stag horn calculus | 1 (0.1) | 0 | 0.1 (-0.1, 0.3) | 0 | 0 |

| Preferred Term | ECZTRA-1+2 Tralokinumab N=1194 n (%) | ECZTRA-1+2 Placebo N=396 n (%) | Risk Difference (95% CI)1 | ECZTRA-3 Tralokinumab N=252 n (%) | ECZTRA-3 Placebo N=126 n (%) |
|---|---|---|---|---|---|
| Status asthmaticus | 1 (0.1) | 0 | 0.1 (-0.1, 0.3) | 0 | 0 |
| Upper limb fracture | 1 (0.1) | 0 | 0.1 (-0.1, 0.3) | 0 | 0 |
| Anaphylactic reaction | 0 | 0 | 0.0 (0.0, 0.0) | 1 (0.4) | 0 |
| Gastroduodenitis | 0 | 0 | 0.0 (0.0, 0.0) | 1 (0.4) | 0 |
| Bronchospasm | 0 | 0 | 0.0 (0.0, 0.0) | 0 | 1 (0.8) |
| Dermatitis infected | 0 | 0 | 0.0 (0.0, 0.0) | 0 | 1 (0.8) |
| Herpes zoster | 0 | 0 | 0.0 (0.0, 0.0) | 0 | 1 (0.8) |
| Meningitis aseptic | 0 | 0 | 0.0 (0.0, 0.0) | 0 | 1 (0.8) |
| Dermatitis exfoliative generalized | 2 (0.2) | 1 (0.3) | -0.1 (-0.6, 0.4) | 0 | 0 |
| Asthma | 1 (0.1) | 1 (0.3) | -0.2 (-0.7, 0.3) | 0 | 0 |
| Bronchitis | 1 (0.1) | 1 (0.3) | -0.2 (-0.7, 0.3) | 0 | 0 |
| ~~Abdominal pain~~ | ~~0~~ | ~~1 (0.3)~~ | ~~-0.3 ( 0.8, 0.2)~~ | ~~0~~ | ~~0~~ |
| ~~Accelerated hypertension~~ | ~~0~~ | ~~1 (0.3)~~ | ~~-0.3 ( 0.8, 0.2)~~ | ~~0~~ | ~~0~~ |
| ~~Cataract subcapsular~~ | ~~0~~ | ~~1 (0.3)~~ | ~~-0.3 ( 0.8, 0.2)~~ | ~~0~~ | ~~0~~ |
| ~~Chronic obstructive pulmonary disease~~ | ~~0~~ | ~~1 (0.3)~~ | ~~-0.3 ( 0.8, 0.2)~~ | ~~0~~ | ~~0~~ |
| ~~Deep vein thrombosis~~ | ~~0~~ | ~~1 (0.3)~~ | ~~-0.3 ( 0.8, 0.2)~~ | ~~0~~ | ~~0~~ |
| ~~Erysipelas~~ | ~~0~~ | ~~1 (0.3)~~ | ~~-0.3 ( 0.8, 0.2)~~ | ~~0~~ | ~~0~~ |
| ~~Erythema~~ | ~~0~~ | ~~1 (0.3)~~ | ~~-0.3 ( 0.8, 0.2)~~ | ~~0~~ | ~~0~~ |
| ~~Osteoarthritis~~ | ~~0~~ | ~~1 (0.3)~~ | ~~-0.3 ( 0.8, 0.2)~~ | ~~0~~ | ~~0~~ |
| ~~Pericarditis~~ | ~~0~~ | ~~1 (0.3)~~ | ~~-0.3 ( 0.8, 0.2)~~ | ~~0~~ | ~~0~~ |
| ~~Pilonidal cyst~~ | ~~0~~ | ~~1 (0.3)~~ | ~~-0.3 ( 0.8, 0.2)~~ | ~~0~~ | ~~0~~ |
| ~~Polymyalgia rheumatica~~ | ~~0~~ | ~~1 (0.3)~~ | ~~-0.3 ( 0.8, 0.2)~~ | ~~0~~ | ~~0~~ |
| ~~Skin infection~~ | ~~0~~ | ~~1 (0.3)~~ | ~~-0.3 ( 0.8, 0.2)~~ | ~~0~~ | ~~0~~ |
| ~~Spinal osteoarthritis~~ | ~~0~~ | ~~1 (0.3)~~ | ~~-0.3 ( 0.8, 0.2)~~ | ~~0~~ | ~~0~~ |

Source: Clinical data safety reviewer for BLA 761180, adae.xpt; software: Python.
Treatment-emergent adverse events defined as an event starting after first use of the investigational medicinal product.
[1] Risk difference column shows absolute difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: CI, confidence interval; N, number of subjects in group; n, number of subjects with adverse event; PT, preferred term; MedDRA, Medical Dictionary for Regulatory Activities

## Maintenance Treatment Period

During the maintenance treatment period, the most frequently reported SAEs were in the tralokinumab Q4W group in the monotherapy trials and in the placebo group in ECZTRA-3, as presented in Table 28.

No more than two SAEs in any SOC were reported for the tralokinumab or placebo groups. The SOCs with two SAEs were infections and infestations, respiratory, thoracic and mediastinal disorders, and injury, poisoning and procedural complications.

Refer to the SAE narratives for subjects in the tralokinumab treatment groups during the maintenance treatment period in Section III.17. Most SAEs were assessed by the Investigators/Applicant were *not related*. The only SAE assessed by the Investigator as *possibly related* was gastroenteritis clostridial, in subject (b) (6)

**Table 28. SAEs, Safety Population, Trials ECZTRA-1, ECZTRA-2, and ECZTRA-3 (Maintenance Treatment Period)**

| Preferred Term | ECZTRA-1+2 Tralokinumab Q2W N=159 n (%) | ECZTRA-1+2 Tralokinumab Q4W N=165 n (%) | ECZTRA-1+2 Placebo N=141 n (%) | ECZTRA-3 Tralokinumab Q2W N=243 n (%) | ECZTRA-3 Tralokinumab Q4W N=69 n (%) | ECZTRA-3 Placebo N=41 n (%) |
|---|---|---|---|---|---|---|
| Any SAE | 1 (0.6) | 6 (3.6) | 1 (0.7) | 5 (2.1) | 0 | 1 (2.4) |
| Diverticulitis | 1 (0.6) | 0 | 0 | 0 | 0 | 0 |
| Asthma | 0 | 1 (0.6) | 1 (0.7) | 0 | 0 | 0 |
| Intervertebral disc protrusion | 0 | 1 (0.6) | 0 | 0 | 0 | 0 |
| Pneumonia | 0 | 1 (0.6) | 0 | 0 | 0 | 0 |
| Pneumothorax spontaneous | 0 | 1 (0.6) | 0 | 0 | 0 | 0 |
| Dizziness | 0 | 1 (0.6) | 0 | 0 | 0 | 0 |
| Papillary thyroid cancer | 0 | 1 (0.6) | 0 | 0 | 0 | 0 |
| Schizophrenia | 0 | 1 (0.6) | 0 | 0 | 0 | 0 |
| Appendicitis | 0 | 0 | 0 | 1 (0.4) | 0 | 0 |
| Depression | 0 | 0 | 0 | 1 (0.4) | 0 | 0 |
| Gastroenteritis clostridial | 0 | 0 | 0 | 1 (0.4) | 0 | 0 |
| Hypoglycemia | 0 | 0 | 0 | 1 (0.4) | 0 | 0 |
| Ligament rupture | 0 | 0 | 0 | 1 (0.4) | 0 | 0 |
| Wrist fracture | 0 | 0 | 0 | 1 (0.4) | 0 | 0 |
| Invasive ductal breast carcinoma | 0 | 0 | 0 | 0 | 0 | 1 (2.4) |

Source: Clinical data safety reviewer for BLA 761180, adae.xpt; software: Python.
Treatment-emergent adverse events defined as an event starting after the first use of the investigational medicinal product.
Abbreviations: ECZTRA, ECZema TRAlokinumab; N, number of subjects in treatment arm; n, number of subjects with adverse event; Q2W, every 2 weeks; Q4W, every 4 weeks; SAE, serious adverse event

## Open-Label Treatment Period

During the open-label treatment period of the pooled monotherapy trials, SAEs were most frequently reported for the SOC of infections and infestations (0.7%).

SAEs were reported in at least one subject for the tralokinumab Q2W+optional TCS group (n=1121) for the following PTs: cellulitis (2), dermatitis atopic (3), syncope (2), acute myocardial infarction (3), invasive breast carcinoma (2), and anaphylactic reaction (2).

Refer to the summary of SAE narratives for subjects in the tralokinumab treatment groups during the open-label treatment period in Section III.17. Most SAEs were assessed by the Investigators/Applicant as *not related*. The following SAEs were assessed by the Investigators as *possibly related* or *probably related*:

- ECZTRA-1: Dermatitis atopic - Subject: (b) (6); cellulitis (2) - Subjects: (b) (6) and (b) (6) invasive breast carcinoma (2) - Subjects: (b) (6) and (b) (6) cystitis - Subject: (b) (6) dermatomyositis - Subject: (b) (6) eosinophilia - Subject: (b) (6) furuncle - Subject: (b) (6) hepatitis - Subject: (b) (6) ulcerative keratitis - Subject: (b) (6) venous thrombosis - Subject: (b) (6) (subject also had an SAE of cellulitis).

- ECZTRA-2: Benign ethnic neutropenia - Subject: (b) (6) keratitis viral - Subject: (b) (6)

***Reviewer's Comment***

*This reviewer agrees with the Investigators' assessments as "probably related or possibly related" for the SAEs listed above, as causality could not be ruled out based on the narratives of clinical cases and on tralokinumab's mechanism of action.*

## Dropouts and/or Discontinuations Due to Adverse Events, ECZTRA-1, ECZTRA-2, and ECZTRA-3

### Initial Treatment Period

During the initial treatment period of the monotherapy trials, AEs leading to treatment discontinuation were balanced between treatment groups and were reported in 2.4% of subjects in the tralokinumab group, compared to 2.8% of subjects in the placebo group (Table 29). The only AEs leading to discontinuations in the tralokinumab group reported in at least one subject, and more frequently than the placebo group, were injection site reactions in four (0.3%) and eosinophilia in three (0.3%) subjects. In addition, narrow FMQ reported AEs of paresthesia and alopecia in three (0.3%) and two (0.2%) subjects, respectively, in the tralokinumab group compared to zero subjects in the placebo group.

The following AEs leading to treatment discontinuation were reported in the tralokinumab group in one subject each: acute left ventricular failure, agitation, alopecia areata, angiosarcoma, conjunctivitis, coronary artery disease, depression suicidal, diffuse alopecia, hyperesthesia, hyperhidrosis, hypoesthesia, ischemic cardiomyopathy, leishmaniasis, livedo reticularis, liver function test increased, night sweats, osteolysis, paresthesia oral, and pneumonia.

During the initial treatment period of ECZTRA-3, AEs leading to treatment discontinuation were more frequent in the tralokinumab group (2.4%) than the placebo group (0.8%). No AE led to discontinuations in at least one subject. The following AEs in the tralokinumab group led to discontinuations in one subject each: injection site reaction, conjunctivitis, anxiety, hernia, influenza, mood altered, myalgia, and otitis media.

**Table 29. Adverse Events Leading to Discontinuation (in at Least One Subject), Safety Population, Trials ECZTRA-1, ECZTRA-2, and ECZTRA-3 (Initial Treatment Period)**

| Preferred Term | ECZTRA-1+2 Tralokinumab N=1194 n (%) | ECZTRA-1+2 Placebo N=396 n (%) | Risk Difference (95% CI)[1] | ECZTRA-3 Tralokinumab N=252 n (%) | ECZTRA-3 Placebo N=126 n (%) |
|---|---|---|---|---|---|
| Any AE leading to discontinuation | 29 (2.4) | 11 (2.8) | -0.4 (-2.2, 1.4) | 6 (2.4) | 1 (0.8) |
| Injection site reaction | 4 (0.3) | 0 | 0.3 (-0.0, 0.6) | 1 (0.4) | 0 |
| Eosinophilia | 3 (0.3) | 0 | 0.3 (0.0, 0.6) | 0 | 0 |
| Dermatitis atopic | 7 (0.6) | 7 (1.8) | -1.2 (-2.6, 0.2) | 0 | 1 (0.8) |

Source: Clinical data safety reviewer for BLA 761180, adae.xpt; software: Python.
Treatment-emergent adverse events defined as events starting after first use of the investigational medicinal product.
[1] Risk difference column shows absolute difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: AE, adverse event; CI, confidence interval; ECZTRA, ECZema TRAlokinumab; N, number of subjects in group; n, number of subjects with adverse event

**Table 30. Adverse Events Leading to Discontinuation (in at Least One Subject) by FDA Medical Query (Narrow), Safety Population, ECZTRA-1, -2, and -3 (Initial Treatment Period)**

| FDA Medical Query (Narrow) | ECZTRA-1+2 Tralokinumab N=1194 n (%) | ECZTRA-1+2 Placebo N=396 n (%) | Risk Difference (95% CI)[1] | ECZTRA-3 Tralokinumab N=252 n (%) | ECZTRA-3 Placebo N=126 n (%) |
|---|---|---|---|---|---|
| Local administration reactions | 4 | | 0.3 | | |
| (narrow FMQ) | (0.3) | 0 | (-0.0, 0.6) | 1 (0.4) | 0 |
| Paresthesia | 3 | | 0.3 | | |
| (narrow FMQ) | (0.3) | 0 | (0.0, 0.6) | 0 | 0 |
| Alopecia | 2 | | 0.2 | | |
| (narrow FMQ) | (0.2) | 0 | (-0.0, 0.4) | 0 | 0 |

Source: Clinical data safety reviewer for BLA 761180, adae.xpt; software: Python.
Treatment-emergent adverse events defined as an event starting after the first use of IMP (investigational medicinal product)
[1] Risk difference column shows absolute difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: AE, adverse event; CI, confidence interval; FDA, Food and Drug Administration; FMQ, FDA Medical Dictionary for Regulatory Affairs query; N, number of subjects in group; n, number of subjects with adverse event

## Maintenance/Continuation Treatment Period

During the maintenance treatment period of the monotherapy trials, AEs that led to discontinuation were more frequent in the pooled tralokinumab Q2W group (1.9% of subjects, 4.7 events/100 subject-years of exposure) compared to the pooled tralokinumab Q4W group (1.2% of subjects, 2.3 events/100 subject-years of exposure) and the pooled placebo group (0% of subjects, 0 events/100 subject-years of exposure).

During the continuation treatment period of ECZTRA-3, the tralokinumab Q2W group (1.2%) and tralokinumab Q4W group (1.4%) reported a lower rate of AEs that led to discontinuation than the placebo group (2.4%). These data are summarized in Table 31.

**Table 31. AEs Leading to Discontinuation, Safety Population, Trials ECZTRA-1, ECZTRA-2, and ECZTRA-3 (Maintenance Treatment Period)**

| Preferred Term | ECZTRA-1+2 Tralokinumab Q2W N=159 n (%) | ECZTRA-1+2 Tralokinumab Q4W N=165 n (%) | ECZTRA-1+2 Placebo N=141 n (%) | ECZTRA-3 Tralokinumab Q2W N=243 n (%) | ECZTRA-3 Tralokinumab Q4W N=69 n (%) | ECZTRA-3 Placebo N=41 n (%) |
|---|---|---|---|---|---|---|
| Any AE leading to discontinuation | 3 (1.9) | 2 (1.2) | 0 | 3 (1.2) | 1 (1.4) | 1 (2.4) |
| Ulcerative keratitis | 1 (0.6) | 0 | 0 | 0 | 0 | 0 |
| Dermatitis atopic | 0 | 1 (0.6) | 0 | 2 (0.8) | 0 | 0 |
| Conjunctivitis allergic | 1 (0.6) | 0 | 0 | 0 | 0 | 0 |
| Injection site reaction | 1 (0.6) | 0 | 0 | 0 | 0 | 0 |
| Papillary thyroid cancer | 0 | 1 (0.6) | 0 | 0 | 0 | 0 |
| Eczema herpeticum | 0 | 0 | 0 | 1 (0.4) | 0 | 0 |
| Prostate cancer | 0 | 0 | 0 | 0 | 1 (1.4) | 0 |
| Invasive ductal breast carcinoma | 0 | 0 | 0 | 0 | 0 | 1 (2.4) |

Source: Clinical data safety reviewer for BLA 761180, adae.xpt; software: Python.
Treatment-emergent adverse events defined as events starting after first use of the investigational medicinal product.
Abbreviations: AE, adverse event; ECZTRA, ECZema TRAlokinumab; N, number of subjects in treatment arm; n, number of subjects with adverse event; Q2W, every 2 weeks; Q4W, every 4 weeks

**Open-Label Treatment Period**

During the open-label treatment period of the monotherapy trials (n=1121), AEs that led to discontinuation were reported in 2.5% of subjects in the pooled tralokinumab Q2W+optional TCS group. The most frequently reported AEs that led to discontinuation were dermatitis atopic (0.5%), injection site reaction (0.4%), and invasive breast carcinoma (0.2%).

The following AEs leading to treatment discontinuation were reported for tralokinumab+optional TCS in the pooled monotherapy trials group, in one subject each: acute myocardial infarction, cellulitis, dermatitis exfoliative, dermatomyositis, eosinophilia, furuncle, hepatic, enzyme increased, hepatitis, lymphadenopathy, neuralgia, edema peripheral, venous thrombosis, alanine aminotransferase increased, aspartate aminotransferase increased, head injury, injection site hypersensitivity, photosensitivity reaction, pyrexia, scleroderma, and urticaria.

## Treatment-Emergent Adverse Events, ECZTRA-1, ECZTRA-2, and ECZTRA-3

**Initial Treatment Period**

During the initial treatment period, TEAEs were reported with similar frequencies in the tralokinumab group compared to the placebo groups in the pooled monotherapy trials (69% versus 71.5%) and ECZTRA-3 trial (71.4 versus 66.7%)

For the pooled monotherapy trials, TEAEs reported in the tralokinumab group with a frequency of ≥1% compared to the placebo group included conjunctivitis, injection site reaction, viral upper respiratory tract infection, allergic conjunctivitis, and pharyngitis. Paresthesia was added based on Narrow and Broad FMQ search. A similar pattern of AEs was reported for ECZTRA-3.

(corresponding to Table 1 of Section 6.1 in the proposed label entitled: “Adverse reactions occurring in ≥1% of the (b) (4) monotherapy group or the (b) (4) TCS group in the atopic dermatitis trials through Week 16”) includes the grouped PTs defined as:

- Upper respiratory tract infection: upper respiratory tract infection, viral upper respiratory tract infection, pharyngitis, and nasopharyngitis (common cold).
- Conjunctivitis: conjunctivitis and allergic conjunctivitis.
- Injection site reaction: pain, erythema, and swelling.
- Eosinophilia: eosinophilia and eosinophil count increased.

**Table 32. Grouped Queries by Preferred Term, Safety Population, ECZTRA-1, ECZTRA-2, and ECZTRA-3 (Initial Treatment Period)**

| Grouped Query<br>Preferred Term | ECZTRA-1+2 Tralokinumab N=1194<br>n (%) | ECZTRA-1+2 Placebo N=396<br>n (%) | Risk Difference (95% CI)[1] | ECZTRA-3 Tralokinumab N=252<br>n (%) | ECZTRA-3 Placebo N=126<br>n (%) |
|---|---|---|---|---|---|
| Conjunctivitis (GQ) | 88 (7.4) | 12 (3.0) | 4.4 (2.2, 6.6) | 33 (13.1) | 6 (4.8) |
| Conjunctivitis | 61 (5.1) | 7 (1.8) | 3.3 (1.5, 5.1) | 28 (11.1) | 4 (3.2) |
| Conjunctivitis allergic | 28 (2.3) | 5 (1.3) | 1.0 (-0.4, 2.4) | 5 (2.0) | 2 (1.6) |
| Upper respiratory tract infection (GQ) | 284 (23.8) | 80 (20.2) | 3.6 (-1.0, 8.2) | 73 (29.0) | 19 (15.1) |
| Viral upper respiratory tract infection | 188 (15.7) | 58 (14.6) | 1.1 (-2.9, 5.1) | 49 (19.4) | 14 (11.1) |
| Pharyngitis | 16 (1.3) | 1 (0.3) | 1.0 (0.2, 1.8) | 2 (0.8) | 0 |
| Upper respiratory tract infection | 68 (5.7) | 19 (4.8) | 0.9 (-1.6, 3.4) | 19 (7.5) | 6 (4.8) |
| Nasopharyngitis | 19 (1.6) | 3 (0.8) | 0.8 (-0.3, 1.9) | 3 (1.2) | 0 |
| Injection site reaction (GQ) | 87 (7.3) | 16 (4.0) | 3.3 (0.9, 5.7) | 27 (10.7) | 1 (0.8) |
| Injection site reaction | 39 (3.3) | 2 (0.5) | 2.8 (1.6, 4.0) | 17 (6.7) | 0 |
| Injection site swelling | 8 (0.7) | 0 | 0.7 (0.2, 1.2) | 0 | 0 |
| Injection site erythema | 12 (1.0) | 2 (0.5) | 0.5 (-0.4, 1.4) | 0 | 0 |
| Injection site induration | 3 (0.3) | 0 | 0.3 (0.0, 0.6) | 0 | 0 |
| Injection site edema | 3 (0.3) | 0 | 0.3 (0.0, 0.6) | 0 | 0 |
| Injection site pain | 32 (2.7) | 10 (2.5) | 0.2 (-1.6, 2.0) | 5 (2.0) | 0 |
| Injection site hypersensitivity | 2 (0.2) | 0 | 0.2 (-0.0, 0.4) | 0 | 0 |
| Injection site mass | 2 (0.2) | 0 | 0.2 (-0.0, 0.4) | 0 | 0 |
| Injection site urticaria | 2 (0.2) | 0 | 0.2 (-0.0, 0.4) | 2 (0.8) | 0 |
| Injection site bruising | 5 (0.4) | 1 (0.3) | 0.1 (-0.5, 0.7) | 0 | 1 (0.8) |
| Injection site hematoma | 1 (0.1) | 0 | 0.1 (-0.1, 0.3) | 3 (1.2) | 0 |
| Injection site pruritus | 3 (0.3) | 1 (0.3) | 0.0 (-0.6, 0.6) | 2 (0.8) | 0 |
| Injection site discoloration | 0 | 0 | 0.0 (0.0, 0.0) | 1 (0.4) | 0 |
| Injection site rash | 0 | 0 | 0.0 (0.0, 0.0) | 1 (0.4) | 0 |
| Injection site hemorrhage | 5 (0.4) | 2 (0.5) | -0.1 (-0.9, 0.7) | 0 | 0 |
| Eosinophilia (GQ) | 17 (1.4) | 2 (0.5) | 0.9 (-0.1, 1.9) | 3 (1.2) | 0 |
| Eosinophilia | 13 (1.1) | 2 (0.5) | 0.6 (-0.3, 1.5) | 1 (0.4) | 0 |
| Eosinophil count increased | 4 (0.3) | 0 | 0.3 (-0.0, 0.6) | 2 (0.8) | 0 |

Source: Clinical data safety reviewer for BLA 761180, adae.xpt; software: Python.
Treatment-emergent adverse events defined as an event starting after the first use of IMP (investigational medicinal product).
[1] Risk difference column shows absolute difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: CI, confidence interval; ECZTRA, ECZema TRAlokinumab; GQ, grouped query; N, number of subjects in treatment arm; n, number of subjects with adverse event

## Maintenance/Continuation Treatment Period

During the maintenance treatment period of the monotherapy trials for responder subjects to tralokinumab treatment at Week 16, TEAEs were more frequent in the pooled tralokinumab Q2W group (73% of subjects, 499.3 events/100 subject-years of exposure) compared to the pooled tralokinumab Q4W group (66.1% of subjects, 414/100 subject-years of exposure) and pooled placebo group (70.4% of subjects, 169/100 subject-years of exposure). Responder subjects to placebo treatment at Week 16 reported TEAEs (56.7% of subjects, 301.7/100 subject-years of exposure) during the maintenance period.

During the continuation treatment period of ECZTRA-3, the frequency of AEs reported for the combined tralokinumab groups (Q2W and Q4W)+TCS (64.8%; 556.5 events/100 subject-years

of exposure) was lower than for the tralokinumab Q2W+TCS group in the initial treatment period (71.4%; 671.7 events/100 subject-years of exposure).

For the tralokinumab responder subjects at Week 16, the frequency of AEs was higher for the tralokinumab Q2W+TCS group (69.6%; 540.5 events/100 subject-years of exposure) compared to the Q4W+TCS group (59.4%; 439.6 events/100 subject-years of exposure).

**Open-Label Treatment Period**

During the open-label treatment period of the monotherapy trials (n=1121), TEAEs were reported in 72.6% of subjects (431.6 events/100 subject-years of exposure) in the pooled tralokinumab Q2W+optional TCS group.

TEAEs reported in ≥2% of subjects included: dermatitis atopic (21.2%, 56.8/100 subject-years of exposure), viral upper respiratory tract infection (17.9%, 42.7/100 subject-years of exposure), upper respiratory tract infection (7%, 15.2/100 subject-years of exposure), conjunctivitis (5.6%, 11.3/100 subject-years of exposure), injection site reaction (3.6%, 15/100 subject-years of exposure), headache (3.2%, 6.9/100 subject-years of exposure), pruritus (3.0%, 6.5/100 subject-years of exposure), back pain (2.4%, 4.5/100 subject-years of exposure), gastroenteritis (2.3%, 3.9/100 subject-years of exposure), herpes simplex (2.2%, 5.1/100 subject-years of exposure), oral herpes (2.1%, 3.6/100 subject-years of exposure), conjunctivitis allergic (2.1%, 4.4/100 subject-years of exposure), diarrhea (2.1%, 3.6/100 subject-years of exposure), and cough (2.0%, 3.5/100 subject-years of exposure).

**Adverse Reactions**

During the initial treatment period of the pooled monotherapy trials, AEs deemed by the Investigators as related to the study drug (adverse reactions [ARs]) and reported at a rate of >1% more frequently in the tralokinumab group compared to the placebo group, included injection site reaction (3.2% versus 0.5%) and conjunctivitis (2.7% versus 1.0%).

During the initial treatment period of the ECZTRA-3 trial, ARs reported at a rate of >1% more frequently in the tralokinumab group compared to the placebo group, included injection site reaction (6.7% versus 0), conjunctivitis (9.1% versus 0.8%), eye pruritus (1.2% versus 0%), sinusitis (2.0% versus 0.8%), injection site pain (1.2% versus 0%), injection site hematoma (1.2% versus 0%), and skin exfoliation (1.2% versus 0%).

During the maintenance/continuation treatment period of the monotherapy pooled trials and ECZTRA-3, ARs were reported at a higher frequency in the tralokinumab Q2W group than the tralokinumab Q4W or placebo group (Table 33).

**Table 33. Adverse Events Assessed by Investigator as Treatment-Related, Safety Population, ECZTRA-1, ECZTRA-2, and ECZTRA-3 (Maintenance/Continuation Treatment Period)**

| Preferred Term | ECZTRA-1+2 Tralokinumab Q2W N=159 n (%) | ECZTRA-1+2 Tralokinumab Q4W N=165 n (%) | ECZTRA-1+2 Placebo N=141 n (%) | ECZTRA-3 Tralokinumab Q2W N=243 n (%) | ECZTRA-3 Tralokinumab Q4W N=69 n (%) | ECZTRA-3 Placebo N=41 n (%) |
|---|---|---|---|---|---|---|
| Any treatment-related AE | 59 (37.1) | 41 (24.8) | 33 (23.4) | 88 (36.2) | 16 (23.2) | 8 (19.5) |
| Dermatitis atopic | 10 (6.3) | 6 (3.6) | 7 (5.0) | 5 (2.1) | 1 (1.4) | 0 |
| Injection site reaction | 9 (5.7) | 11 (6.7) | 1 (0.7) | 12 (4.9) | 4 (5.8) | 0 |
| Viral upper respiratory tract infection | 7 (4.4) | 3 (1.8) | 1 (0.7) | 22 (9.1) | 1 (1.4) | 2 (4.9) |
| Injection site erythema | 6 (3.8) | 5 (3.0) | 0 | 4 (1.6) | 1 (1.4) | 0 |
| Conjunctivitis allergic | 4 (2.5) | 1 (0.6) | 2 (1.4) | 2 (0.8) | 0 | 0 |
| Injection site pain | 5 (3.1) | 0 | 1 (0.7) | 2 (0.8) | 0 | 0 |
| Injection site pruritus | 4 (2.5) | 1 (0.6) | 0 | 2 (0.8) | 0 | 0 |
| Pruritus | 1 (0.6) | 3 (1.8) | 1 (0.7) | 0 | 0 | 0 |
| Conjunctivitis | 4 (2.5) | 3 (1.8) | 0 | 4 (1.6) | 0 | 1 (2.4) |
| Injection site swelling | 3 (1.9) | 1 (0.6) | 0 | 3 (1.2) | 0 | 0 |
| Oral herpes | 2 (1.3) | 1 (0.6) | 2 (1.4) | 5 (2.1) | 3 (4.3) | 1 (2.4) |
| Alanine aminotransferase increased | 1 (0.6) | 2 (1.2) | 1 (0.7) | 2 (0.8) | 1 (1.4) | 0 |
| Headache | 1 (0.6) | 1 (0.6) | 0 | 5 (2.1) | 1 (1.4) | 0 |
| Influenza | 1 (0.6) | 0 | 0 | 2 (0.8) | 0 | 1 (2.4) |
| Upper respiratory tract infection | 4 (2.5) | 2 (1.2) | 0 | 6 (2.5) | 1 (1.4) | 2 (4.9) |
| Herpes zoster | 0 | 0 | 0 | 1 (0.4) | 0 | 1 (2.4) |
| Arthropod bite | 0 | 0 | 0 | 0 | 0 | 1 (2.4) |
| Atrioventricular block first degree | 0 | 0 | 0 | 0 | 0 | 1 (2.4) |
| Keratitis viral | 0 | 0 | 0 | 0 | 0 | 1 (2.4) |

Source: Clinical data safety reviewer for BLA 761180, adae.xpt; software: Python.
Treatment-emergent adverse events defined as events starting after first use of the investigational medicinal product.
[1] Terms included are those that occurred in at least 2% of subjects.
Abbreviations: AE, adverse event; ECZTRA, ECZema TRAlokinumab; N, number of subjects in treatment arm; n, number of subjects with adverse event; Q2W, every 2 weeks; Q4W, every 4 weeks

During the open-label treatment period for the monotherapy pooled trials, ARs were reported in 31.2% of subjects. AEs reported at a >1% frequency were dermatitis atopic (5.2%), conjunctivitis (3.7%), injection site reaction (3.5%), viral upper respiratory tract infection (3.3%), upper respiratory tract infection (1.6%), injection site pain (1.5%), injection site erythema (1.4%), and headache (1.1%).

**TEAE Analysis by Subgroup**

Refer to Section III.17 for a summary of TEAEs by subgroup (sex, age, race/ethnicity, baseline IGA, and region).

## Adverse Events of Special Interest

AESIs were predefined in the protocols for all ECZTRA trials based on the potential and established areas of safety interest for monoclonal antibodies for the treatment of AD, and included:

(1) Eye disorders (conjunctivitis, keratoconjunctivitis, and keratitis).
(2) Skin infections requiring systemic treatment.
(3) Eczema herpeticum.
(4) Malignancies (diagnosed after randomization), excluding basal cell carcinoma, localized squamous cell carcinoma of the skin, and carcinoma in situ of the cervix.

**Eye Disorders (Conjunctivitis, Keratoconjunctivitis, Keratitis)**

The frequency of eye disorders reported during the initial period in the AD pool was higher in the tralokinumab group (7.9%, 31.1/100 patient-years of exposure [PYE]) compared to the placebo group (3.4%, 12.9/100 PYE). Three AEs were severe in the tralokinumab group; none was an SAE (Table 34).

**Table 34. Summary of Eye Disorders by SOC and PT, Initial Treatment Period, AD Pool, Adjusted Pooling, Safety Analysis Set**

**Panel 60 Summary of eye disorders by SOC and PT - initial treatment period - AD pool - adjusted pooling - safety analysis set**

| AESI category<br>System Organ Class (SOC)<br>Preferred term (PT) | Tralokinumab Total (n=1605, PYE=473.19) N | (adj.%) | E | (adj.R) | Placebo Total (n=680, PYE=193.1) N | (adj.%) | E | (adj.R) |
|---|---|---|---|---|---|---|---|---|
| Any AEs | 132 | (7.9) | 155 | 31.1 | 22 | (3.4) | 24 | 12.9 |
| **Conjunctivitis** | **126** | **(7.5)** | **145** | **29.0** | **21** | **(3.2)** | **23** | **12.3** |
| Infections and infestations | 95 | (5.7) | 109 | 21.9 | 15 | (2.2) | 15 | 8.0 |
| Conjunctivitis | 90 | (5.4) | 104 | 21.0 | 13 | (1.9) | 13 | 6.9 |
| Conjunctivitis bacterial | 4 | (0.2) | 4 | 0.7 | 1 | (0.2) | 1 | 0.6 |
| Conjunctivitis viral | 1 | (0.1) | 1 | 0.2 | 1 | (0.1) | 1 | 0.5 |
| Eye disorders | 34 | (2.0) | 36 | 7.1 | 7 | (1.1) | 8 | 4.3 |
| Conjunctivitis allergic | 34 | (2.0) | 36 | 7.1 | 7 | (1.1) | 8 | 4.3 |
| **Keratoconjunctivitis** | **5** | **(0.3)** | **5** | **1.2** | | | | |
| Eye disorders | 5 | (0.3) | 5 | 1.2 | | | | |
| Keratitis | 4 | (0.3) | 4 | 1.0 | | | | |
| Atopic keratoconjunctivitis | 1 | (0.1) | 1 | 0.2 | | | | |
| **Keratitis** | **4** | **(0.2)** | **5** | **0.9** | **1** | **(0.2)** | **1** | **0.6** |
| Eye disorders | 4 | (0.2) | 5 | 0.9 | | | | |
| Keratitis | 4 | (0.2) | 4 | 0.7 | | | | |
| Ulcerative keratitis | 1 | (0.1) | 1 | 0.2 | | | | |
| Infections and infestations | | | | | 1 | (0.2) | 1 | 0.6 |
| Keratitis viral | | | | | 1 | (0.2) | 1 | 0.6 |

AEs collected during the exposure time in the initial treatment period are shown. PYE: Patient years of exposure. N: Number of subjects with one or more events. %: Percentage of subjects with one or more events. adj. %: Adjusted percentage calculated using CMH weights. E: Number of adverse events. R: Rate (number of events divided by patient-years of exposure multiplied by 100). adj. R: Adjusted rate calculated using CMH weights.

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Cross-reference: Modified from M5.3.5.3 ISS AD pool Table 3.1.14

Source: BLA 761180, Module 2.7.4, Section 2.1.6.4.2, Panel 60.

At the end of the trial, a similar proportion of subjects with AESIs of eye disorders during initial period were reported as not recovered/not resolved (19% in the tralokinumab group compared to 21% in the placebo group).

Conjunctivitis was reported at a greater frequency in the tralokinumab group than the placebo group after Week 4 of the initial period. Most subjects with conjunctivitis during the initial period had a history of allergic conjunctivitis or keratoconjunctivitis (56% in the tralokinumab group compared to 71% in the placebo group).

Keratoconjunctivitis was reported in five subjects in the tralokinumab group during the initial period, three of whom had not recovered/ not resolved at the end of trial. Two subjects had a history of allergic conjunctivitis or atopic keratoconjunctivitis. None of the AEs led to permanent discontinuation of treatment.

Keratitis was reported in four subjects in the tralokinumab group during the initial period, one of whom had not recovered/ not resolved at the end of trial. One subject had a history of ulcerative keratitis, and two subjects had a history of both allergic conjunctivitis and atopic keratoconjunctivitis. None of the AEs led to permanent discontinuation of treatment.

The frequency of AESIs of eye disorders reported for the AD pool in the tralokinumab group (14 subjects: 10 conjunctivitis, 1 keratoconjunctivitis, and 3 keratitis) during the follow-up period (4.9/100 PYE) was less than in the initial period (31.1/100 PYE). Two subjects had SAEs (keratitis viral or keratitis bacterial) and five subjects had not recovered/ not resolved at the end of trial.

During the initial period of the monotherapy pool, the types and frequency of reported eye disorder AESIs were similar to those reported during the initial period of the AD pool.

During the maintenance period of the monotherapy pool, the frequency of conjunctivitis reported in the tralokinumab Q2W group (20.1/100 PYE) was lower than that reported in the tralokinumab Q2W group in the initial period (29.6/100 PYE), and higher than the frequencies reported during the maintenance period for the tralokinumab Q4W group, the rerandomized to placebo group (13/100 PYE), and the placebo responder group (3/100 PYE). Seven of the thirty subjects who reported an AE of conjunctivitis during the maintenance period also reported an AE of conjunctivitis during the initial period. Of the three subjects in the tralokinumab Q2W group with keratoconjunctivitis (two atopic keratoconjunctivitis, one keratitis), none was severe or serious and all recovered. One subject in the tralokinumab Q2W group had an AE of keratitis (ulcerative keratitis, severe), which led to permanent discontinuation of study drug and resolution of the AE after 30 days.

During the open-label period of the monotherapy pool, the frequency of eye disorder AESIs reported in the tralokinumab Q2W group (17.9/100 PYE) was lower than that in the tralokinumab Q2W group in the initial period (31.1/100 PYE), with a similar pattern and types of AEs as in the initial period.

Four subjects reported AESIs of keratoconjunctivitis, all were mild, none led to permanent discontinuation of study drug, and two subjects had outcomes of recovered/resolved.

Keratitis was reported in seven subjects, including two SAEs (outcomes of both reported as recovered): keratitis viral (1) with a corneal swab (+) methicillin-susceptible *Staphylococcus aureus* and ulcerative keratitis (1) with corneal swab (+) *S. aureus*. None of the AEs led to permanent discontinuation of study drug, and the outcome was not recovered/not resolved for only one subject.

During the initial period of ECZTRA-3, the frequency of reported eye disorder AESIs were higher in the tralokinumab Q2W+TCS group (13.5%, 52.0/100 PYE) compared to the placebo+TCS group (5.6%, 18.5/100 PYE), and higher in both groups in ECZTRA-3 compared to the initial treatment period of the monotherapy pool. In the tralokinumab+TCS group, no SAE or severe AE was reported, and AESIs were reported as conjunctivitis (38) or keratitis (1), with 38% of subjects reported as not recovered during the trial. One AE of conjunctivitis led to permanent discontinuation of study drug.

During the continuation period of ECZTRA-3, for the tralokinumab Q2W+TCS group, the frequency of reported eye disorder AESIs was lower (11.4/100 PYE) compared to the initial period (52.0/100 PYE) with a similar pattern and types of reported AESIs.

For responder subjects at Week 16 who were in the tralokinumab Q2W+TCS during the initial period, eye disorder AESIs were reported with a higher frequency in the tralokinumab Q2W+TCS group (4.3%, 14.0/100 PYE) compared to the tralokinumab Q4W+TCS group (1.4%, 4.8/100 PYE).

**Skin Infections Requiring Systemic Treatment**

The reported frequency of this AESI was lower in the tralokinumab group compared to the placebo group in the initial period and decreased in the tralokinumab group from the initial period to maintenance/continuation and open-label periods (Table 35).

**Table 35. Frequency of Skin Infections Requiring Systemic Treatment per 100 PYE or Incidence (%)**

| Pool/Treatment Period | Tralokinumab Group | Placebo Group |
|---|---|---|
| AD pool, initial | 9.7(2.6%) | 22.8(5.5%) |
| AD pool, follow-up | 1.7 | |
| Monotherapy, initial | 10.7 (2.8%) | 27.1 (6.6%) |
| Monotherapy, maintenance | 4.7 | |
| Monotherapy, open-label | 7.1 | |
| ECZTRA-3 (+TCS), initial | 5.3 (1.6%) | 23.7 (5.6%) |
| ECZTRA-3 (+TCS), continuation | 1.4 | |

Source: BLA 761180, Module 2.7.4, Section 2.1.6.1.
Abbreviations: AD, atopic dermatitis; ECZTRA, ECZema TRAlokinumab; PYE, person-years of exposure; TCS, topical corticosteroids

Three SAEs in this AESI category were reported in the tralokinumab group of ECZTRA-1: Subjects (b) (6) (cellulitis), (b) (6) (injection site reaction/possible cellulitis), and (b) (6) (leishmaniasis) and the placebo group each. Refer to Section III.17 for details.

*Eczema Herpeticum*

The reported frequency of eczema herpeticum was lower in the tralokinumab group compared to the placebo group in the initial period and remained stable or decreased in the tralokinumab group from the initial period to the maintenance/continuation and open-label periods (Table 36).

**Table 36. Frequency of Eczema Herpeticum per 100 PYE or Incidence (%)**

| Pool/Treatment Period | Tralokinumab Group | Placebo Group |
|---|---|---|
| AD pool, initial | 1.2 (0.3%) | 5.2 (1.5%) |
| AD pool, follow-up | 0.7 | |
| Monotherapy, initial | 1.4 (0.4%) | 6.1 (1.8%) |
| Monotherapy, maintenance | 1.2 | |
| Monotherapy, open-label | 1.4 | |
| ECZTRA-3 (+TCS), initial | 1.3 (0.4%) | 2.6 (0.8%) |
| ECZTRA-3 (+TCS), continuation | 1.4 | |

Source: BLA 761180, Module 2.7.4, Section 2.1.6.2.
Abbreviations: AD, atopic dermatitis; ECZTRA, ECZema TRAlokinumab; PYE, person-years of exposure; TCS, topical corticosteroids

## Malignancies

In addition to malignancies prespecified as AESIs, the Applicant included basal cell carcinoma, localized skin squamous cell carcinoma, and carcinoma in situ of the cervix diagnosed after randomization and reported during the entire trial and safety follow-up periods in the AD pool using the standardized MedDRA Query (SMQ) of "Malignant or unspecified tumors (narrow scope) (MedDRA code 20000091)."

The frequency of reported malignancies was similar in the tralokinumab group (0.9%; 1.4/100 patient years of observation [PYO]) compared to the placebo group (0.7%; 2.2/ 100 PYO). Of the 31 reported AEs of malignancies (24 in the tralokinumab group and 7 in the placebo group), most were reported under high level term (HLT) of "Skin neoplasms malignant and unspecified (excl melanoma)" with no clustering over time or in other organ systems (Table 37).

**Table 37. Summary of Malignancies (SMQ) by SOC and PT, Entire Trial Period, AD Pool, Simple Pooling, Safety Analysis Set**

| System Organ Class (SOC) Preferred term (PT) | Tralokinumab (n=1991, PYO=1690.9) N | (%) | E | R | Placebo (n=761, PYO=316.59) N | (%) | E | R |
|---|---|---|---|---|---|---|---|---|
| Any AEs | 17 | (0.9) | 24 | 1.4 | 5 | (0.7) | 7 | 2.2 |
| Serious | 5 | (0.3) | 5 | 0.3 | 2 | (0.3) | 2 | 0.6 |
| Severe | 3 | (0.2) | 3 | 0.2 | 1 | (0.1) | 1 | 0.3 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 17 | (0.9) | 24 | 1.4 | 5 | (0.7) | 7 | 2.2 |
| Squamous cell carcinoma of skin | 8 | (0.4) | 13 | 0.8 | 1 | (0.1) | 3 | 0.9 |
| Basal cell carcinoma | 3 | (0.2) | 3 | 0.2 | 1 | (0.1) | 1 | 0.3 |
| Bowen's disease | 3 | (0.2) | 3 | 0.2 | | | | |
| Invasive breast carcinoma | 2 | (0.1) | 2 | 0.1 | | | | |
| Angiosarcoma | 1 | (0.1) | 1 | 0.1 | | | | |
| Papillary thyroid cancer | 1 | (0.1) | 1 | 0.1 | | | | |
| Prostate cancer | 1 | (0.1) | 1 | 0.1 | | | | |
| Breast cancer metastatic | | | | | 1 | (0.1) | 1 | 0.3 |
| Cervix carcinoma stage 0 | | | | | 1 | (0.1) | 1 | 0.3 |
| Invasive ductal breast carcinoma | | | | | 1 | (0.1) | 1 | 0.3 |

AEs collected during the observation time in the initial, maintenance, open-label and safety follow-up periods are shown, assigned to the latest treatment administered before onset of the AE. The same subject may contribute to more than one column. Classification according to MedDRA 20.0. PYO: Patient years of observation. n: Number of subjects. N: Number of subjects with observation. %: 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).

Source: BLA 761180, Module 2.7.4, Panel 64 (page 194).
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; SMQ, standardized MedDRA query

In addition, three subjects in the tralokinumab group were reported with a malignancy after completion or early termination of the trial:

(1) ECZTRA-1, Subject (b) (6): A 50-year-old male subject diagnosed with cutaneous T-cell lymphoma on Day 134 of the open-label period (92 days after last dose). The Investigator

assessment was that the cutaneous T-cell lymphoma was likely present for years (misdiagnosed as AD). The subject died of pneumonia on Day 450 of the open-label period.

(2) ECZTRA-2, Subject (b) (6): A 24-year-old female subject treated with tralokinumab for 334 days diagnosed with poorly differentiated metastatic squamous cell carcinoma left lateral tongue and died 677 days after the first dose of tralokinumab.
(3) ECZTRA-3, Subject (b) (6): A 79-year-old female subject diagnosed with malignant melanoma (pT1a, left thigh) during a routine dermatologic appointment (Day 565 after first dose and Day 355 after last dose of tralokinumab+TCS), underwent wide local excision of the melanoma. Causality per Investigator/Applicant was not related to tralokinumab.

## Safety Areas of Interest

Safety areas of interest were defined based on the known risks/AEs associated with the administration of monoclonal antibodies, the mechanism of action of tralokinumab (IL-13 inhibition), and regulatory interest, and comprised the following:

(1) Injection site reactions.
(2) Severe or serious infections (including OIs, tuberculous infections, or clinical endoparasitosis).
(3) Anaphylaxis and serious allergic reactions.
(4) Immune complex disease.
(5) Medication errors.
(6) Suicidality and psychiatric disorders.
(7) Cardiovascular AEs of interest.
(8) Rare AEs.

### Injection Site Reactions

The Applicant conducted a MedDRA search for injection site reactions, using the following HLT/MedDRA codes: administration site reactions NEC (primary and secondary terms) (10057196), application and instillation site reactions (primary and secondary terms) (10003057), and injection site reactions (primary and secondary terms) (10022097).

During the initial treatment period in the AD pool, the frequency of injection site reactions was higher in the tralokinumab group (7.2%; 51.5/100 PYE) compared to the placebo group (3.0%; 21.3/100 PYE).

In the tralokinumab group, one SAE (ECZTRA-1/13103), two severe AEs, and five discontinuations due to injection site reactions were reported (four of the five subjects had previous injection site reactions).

In the monotherapy pool, the frequency of injection site reactions with tralokinumab Q2W was higher during the maintenance period (99.1/100 PYE) than the initial period (56.1/100 PYE).

During the maintenance period in the monotherapy pool, the frequency of injection site reactions correlated with the dosing groups (tralokinumab Q2W: 99.1/100 PYE; tralokinumab Q4W: 43.4/100 PYE; subjects rerandomized to placebo: 13.1/100 PYE; placebo responders: 3.4/100 PYE). No SAE or severe AE was reported.

The frequency of injection site reactions reported during the open-label period in the monotherapy pool (37.0/100 PYE) was lower than in the initial treatment period (56.1/100 PYE).

During the initial period of the tralokinumab+TCS study (ECZTRA-3), the frequency of injection site reactions reported was higher in the tralokinumab Q2W+TCS group (10.7%; 61.3/100 PYE) compared to the placebo+TCS group (0.8%; 2.6/100 PYE). No SAE or severe AE was reported.

During the continuation period of the tralokinumab+TCS study (ECZTRA-3), the frequency of injection site reactions reported for the combined (Q2W and Q4W) tralokinumab+TCS groups (71.0/100 PYE) was similar to the frequency reported for the tralokinumab Q2W+TCS group in the initial period (61.3/100 PYE).

**Severe or Serious Infections—OIs, Tuberculosis, Clinical Endoparasitosis**

In the AD pool, the adjusted rates of any severe infection, serious infection, infection requiring treatment with parenteral antibiotics, infection requiring treatment with oral antibiotics/antivirals/antifungals for >2 weeks, OI, clinical endoparasitosis, and tuberculous infection were lower in the tralokinumab group compared to the placebo group in the initial period. The rate for each category decreased in the tralokinumab group during the safety follow-up period compared to the initial period (Table 38).

**Table 38. Summary of Treatment-Emergent Severe or Serious Infection, Initial Treatment Period and Follow-up, AD Pool, Safety Analysis Set**

| | Initial treatment period (16 weeks[a]) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Tralokinumab (n=1605; PYE=473.19) | | | | Placebo (n=680; PYE=193.1) | | | |
| | N | (adj.%) | E | adj.R | N | (adj.%) | E | adj.R |
| Any severe infection | 10 | (0.6) | 10 | 2.1 | 9 | (1.4) | 11 | 5.8 |
| Any serious infection | 6 | (0.4) | 6 | 1.3 | 7 | (1.1) | 7 | 3.7 |
| Any infection requiring treatment with parenteral antibiotics | 8 | (0.4) | 9 | 1.7 | 5 | (0.7) | 5 | 2.5 |
| Any infection requiring treatment with oral antibiotics/antivirals/ antifungal for more than 2 weeks | 15 | (0.9) | 15 | 3.2 | 14 | (2.2) | 15 | 8.3 |
| Any opportunistic infection | 56 | (3.4) | 64 | 13.0 | 32 | (4.9) | 40 | 21.3 |
| Any clinical endoparasitosis | 0 | (0.0) | 0 | 0.0 | 0 | (0.0) | 0 | 0.0 |
| Any tuberculous infection | 0 | (0.0) | 0 | 0.0 | 0 | (0.0) | 0 | 0.0 |
| | **Safety follow-up period (up to 14 weeks)** | | | | | | | |
| | Tralokinumab (n=1456; PYFU=286.99) | | | | Placebo (n =252; PYFU=43.85) | | | |
| | N | (%) | E | R | N | (%) | E | R |
| Any severe infection | 5 | (0.3) | 6 | 2.1 | 0 | (0.0) | 0 | 0.0 |
| Any serious infection | 6 | (0.4) | 7 | 2.4 | 0 | (0.0) | 0 | 0.0 |
| Any infection requiring treatment with parenteral antibiotics | 2 | (0.1) | 3 | 1.0 | 0 | (0.0) | 0 | 0.0 |
| Any infection requiring treatment with oral antibiotics/antivirals/ antifungal for more than 2 weeks | 5 | (0.3) | 5 | 1.7 | 1 | (0.4) | 1 | 2.3 |
| Any opportunistic infection | 11 | (0.8) | 11 | 3.8 | 5 | (2.0) | 7 | 16.0 |
| Any clinical endoparasitosis | 0 | (0.0) | 0 | 0.0 | 0 | (0.0) | 0 | 0.0 |
| Any tuberculous infection | 0 | (0.0) | 0 | 0.0 | 0 | (0.0) | 0 | 0.0 |

**Abbreviations:** adj. R = adjusted rate calculated using CMH weights; adj. % = adjusted percentage calculated using CMH weights; E = number of adverse events; n = number of subjects; N = number of subjects with one or more events; PYE = patient years of exposure; PYFU = patient years of follow-up; R = rate (number of events divided by patient-years of exposure/follow-up multiplied by 100); % = percentage of subjects with one or more events

**Notes:** An event may be captured by multiple searches; a = the initial treatment period was 12 weeks in the dose-finding trial

**Cross-reference:** Modified from M5.3.5.3 ISS AD pool Tables 3.5.10, 3.5.12, 3.5.16, 3.5.18, 3.5.20, 3.5.22, 3.5.24, 3.6.7, 3.6.9, 3.6.11, 3.6.13, 3.6.15, 3.6.17, and 3.6.19

Source: BLA 761180, Module 2.7.4, Section 2.1.6.2, Panel 51.

Four SAEs in this area of special interest were reported in four subjects during the initial period.

Reports of pneumonia (Subject ECZTRA (b) (6)), bronchitis (Subject ECZTRA- (b) (6), and leishmaniasis (Subject ECZTRA- (b) (6) are described in Section III.17.

Infective arthritis (Subject ECZTRA (b) (6) was reported for a prosthetic knee infection triggered by a fall and required operative removal of prosthetic and discontinuation from trial. The outcome was reported as recovering/resolving at the end of the trial.

For AEs in this safety area of special interest, the frequencies of AEs in each category reported during the initial periods of the monotherapy pool and combination (+TCS) trial were similar to those reported during the initial period of the AD pool, and remained stable or decreased in the tralokinumab group over the maintenance/open-label or continuation periods.

**Severe Infections**

Severe infections reported during the initial treatment period of the AD pool in the tralokinumab group included conjunctivitis (in three subjects), and the following AEs in one subject each: arthritis infective, tooth abscess, pneumonia, bronchitis, *Campylobacter* gastroenteritis, influenza, and leishmaniasis.

The frequency of reported severe infections in the tralokinumab group during the safety follow-up period (six AEs in five subjects: septic shock/pneumonia (fatal), keratitis bacterial, eczema herpeticum, endocarditis, and tonsillitis) was similar to the initial treatment period (2.1/100 patient-years of follow-up [PYFU] or PYE).

**Serious Infections**

Serious infections during the initial treatment period of the AD pool were reported at a lower frequency in the tralokinumab group (0.4%, 1.3/100 PYE) compared to the placebo group (1.1%, 3.7/100 PYE). No serious infection was reported in at least one subject in any group. Serious infections in the tralokinumab group included the following AEs: arthritis infective, gastroenteritis viral, pneumonia, bronchitis, cellulitis, and leishmaniasis.

Serious infections in the tralokinumab group during safety follow-up (seven AEs in six subjects: septic shock/pneumonia(fatal), keratitis viral, staphylococcal abscess, and the three listed under severe infections above) were reported at a higher frequency (2.4/100 PYE) than during the initial treatment period (1.3/100 PYE), but at a lower frequency than in the placebo group during the initial treatment period (3.7/100 PYE).

**Opportunistic Infections**

OIs were reported at a lower frequency in the tralokinumab group (3.4%, 13.0/100 PYE). compared to the placebo group (4.9%, 21.3/100 PYE) during the initial treatment period in the AD pool. Most OIs were reported under the HLT of herpes viral infections. The PT of herpes simplex was reported at a higher frequency (1.3% versus 0.9%; 5.2 versus 3.7/100 PYE), and the PTs of oral herpes (0.8% versus 1.6%; 3.1 versus 8.1/100 PYE), herpes zoster (0.4% versus 0.6%; 1.4 versus 2.0/100 PYE), and eczema herpeticum (0.3% versus 1.5%; 1.2 versus 5.2/100 PYE) were reported at a lower frequency in the tralokinumab group compared to the placebo group during the initial treatment period.

The frequency of reported OIs in the monotherapy pool during the initial treatment period for tralokinumab (3.5%, 13.5/100 PYE) compared to the placebo group (5.6%, 25.3/100 PYE) was similar to the reported frequency of OIs during the initial treatment period in the AD pool.

The frequency of reported OIs in the monotherapy pool for the tralokinumab Q2W group in the maintenance period (9.4/100 PYE) and the open-label group (14.6/100 PYE) was similar to that during the initial treatment period (13.5/100 PYE).

The frequency of reported OIs in the tralokinumab+TCS study (ECZTRA-3) during the initial treatment period was similar for tralokinumab (4.4%, 17.3/100 PYE) compared to placebo (4.0%, 15.8/100 PYE), and higher than the reported frequency of OIs during the initial treatment period in the AD pool. All OIs reported were reported under the HLT of herpes viral infections (including oral herpes, herpes simplex, herpes zoster, and eczema herpeticum).

The frequency of reported OIs in ECZTRA-3 for the combined tralokinumab+TCS group in the continuation period (28.4/100 PYE) was higher than the frequency of OIs in the tralokinumab Q2W+TCS group during the initial treatment period (17.3/100 PYE).

**Clinical Endoparasitosis**

No AE of clinical endoparasitosis was reported by the MedDRA search in any treatment group, for any treatment or safety follow-up periods in the AD trials. In the asthma trial (STRATOS 2), one AE of helminthic infection in a subject in the tralokinumab Q2W group was reported during the safety follow-up period.

**Tuberculosis**

No AEs of tuberculous were reported by the MedDRA search in any treatment group, for any treatment or safety follow-up period in the AD trials.

The 120-day safety update for AESI (ISS-AD pool) listed a 26-year-old male subject (ECZTRA-(b) (6) who was treated with placebo+TCS in the initial period and tralokinumab Q2W+TCS during the continuation period reported with tuberculous of mild severity (a positive QuantiFERON test) during the safety follow-up period (deemed *possibly related* to the study drug by the Investigator) with the outcome reported as unknown.

In the asthma trial (STRATOS 2), one AE of *pulmonary tuberculosis* (in a subject who was treated for pulmonary tuberculosis at trial entry) was reported during treatment in the tralokinumab Q2W group.

**Anaphylaxis and Serious Allergic Reactions**

The Applicant applied MedDRA searches for anaphylaxis (SMQ anaphylactic reaction, MedDRA code 20000021 for narrow and broad terms within 2 days of drug administration) and serious hypersensitivity reactions (SMQ hypersensitivity, narrow, MedDRA code 20000214).

No AE of anaphylaxis was reported in the AD pool for the entire trial period.

In the asthma pool, MedDRA search for anaphylaxis captured six AEs (in three subjects) in the tralokinumab group and four AEs (in two subjects) in the placebo total group, with similar frequencies in tralokinumab (0.2%; 0.38/100 PYE) and placebo groups (0.2%; 0.44/100 PYE). No SAEs or severe AEs were reported. The AEs reported in the tralokinumab group included a nonserious AE of anaphylaxis (circulatory collapse) in one subject and two serious allergic reactions (pharyngeal edema and swollen tongue) in one subject following the first dose of tralokinumab. One hypersensitivity reaction suspected to be anaphylaxis was reported after IV administration of tralokinumab in the Phase 2 asthma trial CAT-354-0603.

During the initial period in the AD pool, serious allergic reactions were reported at similar frequencies in the tralokinumab (1.5/100 PYE) and placebo (2.1/100 PYE) groups (Table 39).

**Table 39. Summary of Serious Allergic Reactions by SOC and PT, Initial Treatment Period, AD Pool, Adjusted Pooling, Safety Analysis Set**

| System Organ Class (SOC) Preferred term (PT) | Tralokinumab Total (n=1605, PYE=473.19) N | (adj.%) | E | (adj.R) | Placebo Total (n=680, PYE=193.1) N | (adj.%) | E | (adj.R) |
|---|---|---|---|---|---|---|---|---|
| Any AEs | 8 | (0.4) | 8 | 1.5 | 4 | (0.6) | 4 | 2.1 |
| Skin and subcutaneous tissue disorders | 7 | (0.4) | 7 | 1.3 | 2 | (0.3) | 2 | 1.1 |
| Dermatitis atopic | 5 | (0.3) | 5 | 0.9 | 1 | (0.2) | 1 | 0.6 |
| Dermatitis exfoliative generalised | 2 | (0.1) | 2 | 0.4 | 1 | (0.2) | 1 | 0.6 |
| Immune system disorders | 1 | (0.1) | 1 | 0.2 | | | | |
| Anaphylactic reaction | 1 | (0.1) | 1 | 0.2 | | | | |
| Infections and infestations | | | | | 1 | (0.1) | 1 | 0.5 |
| Dermatitis infected | | | | | 1 | (0.1) | 1 | 0.5 |
| Respiratory, thoracic and mediastinal disorders | | | | | 1 | (0.1) | 1 | 0.5 |
| Bronchospasm | | | | | 1 | (0.1) | 1 | 0.5 |

AEs collected during the exposure time in the initial treatment period are shown. n: Number of subjects. PYE: Patient years of exposure. N: Number of subjects with one or more events. %: Percentage of subjects with one or more events. adj. %: Adjusted percentage calculated using CMH weights. E: Number of adverse events. R: Rate (number of events divided by patient-years of exposure multiplied by 100). adj. R: Adjusted rate calculated using CMH weights.

Source: BLA 761180, Module 2.7.4, Section 2.1.6.6.3, Panel 67.
Abbreviations: AD, atopic dermatitis; AE, adverse event; PT, preferred term; SOC, system organ class

Of the eight AEs in the tralokinumab group in the AD pool, seven were severe AEs, five were *dermatitis atopic* (related to a flare of the underlying AD), two were *dermatitis exfoliative generalized* (Subjects ECZTRA[(b) (6)], ECZTRA-[(b) (6)], and one was *anaphylaxis food allergy* reported as *anaphylactic reaction* (Subject ECZTRA[(b) (6)] Refer to the SAE listings in Section III.17 for details.

The tralokinumab group in the AD pool reported seven serious allergic reactions during the safety follow-up period, for a higher frequency (2.4/100 PYFU) compared to the initial period (1.5/100 PYE). Of the seven AEs, three were *dermatitis atopic* (flare), two were *dermatitis exfoliative generalized* (Subjects ECZTRA[(b) (6)], ECZTRA-[(b) (6)], one was *angioedema* (related to lisinopril, Subject ECZTRA[(b) (6)], and one was *bronchospasm* in a subject with asthma and chronic obstructive pulmonary disease (Subject ECZTRA-[(b) (6)].

In the monotherapy trials, no serious allergic reaction was reported during the maintenance period, and five serious allergic reactions, three AD flares and two SAEs of *anaphylactic reaction* (Subjects ECZTRA-[(b) (6)] bee sting; ECZTRA-[(b) (6)] salmon pizza), were reported during the open-label period. Refer to Section III.17 for details.

No serious allergic reaction was reported in the continuation period of ECZTRA-3.

**Immune Complex Disease**

The Applicant applied MedDRA searches for immune complex disease (SMQ: vasculitis, broad, MedDRA code 20000174; PT: glomerulonephritis, MedDRA code 10018364; PT: immune complex level increased, MedDRA code 10064650; PT: type III immune complex-mediated reaction, MedDRA code 10053614).

In the AD pool of all trial periods, the Applicant did not identify any immune complex disease or serum-sickness reactions for tralokinumab.

In the asthma pool, the frequency of reported AEs related to immune complex disease was similar in the tralokinumab group (0.2%; 0.3/100 PYE) and placebo group (0.1%; 0.1/100 PYE). Of the four AEs (in three subjects) in the tralokinumab group, one SAE (eosinophilic granulomatosis with polyangiitis) led to discontinuation of study drug, and the outcomes of three nonsevere AEs related to vasculitis were reported as recovered. None was considered related to the study drug by the Investigator.

**Medication Errors**

The Applicant conducted a MedDRA search for the SMQ Medication error (broad scope) (MedDRA code 20000224).

In the AD pool of all trial periods, no subject in the tralokinumab group was reported with a medication error or a related AE. Three subjects randomized to the placebo group received at least one dose of tralokinumab (and were assigned to the tralokinumab group in safety analyses), and one subject randomized to the tralokinumab group received a dose of placebo at Week 2 and was reported with severe AEs of PTs dermatitis atopic and dermatitis exfoliative 20 days later.

**Suicidality and Psychiatric Disorders**

The Applicant conducted a MedDRA search for the SMQ suicide/self-injury (narrow scope) (MedDRA code 20000037).

In the AD pool of all trials, two subjects (ECZTRA-(b) (6) and ECZTRA-(b) (6)) in the tralokinumab Q2W group were reported with SAEs (not related to study drug) related to suicidality in the initial period. Refer to Section III.17 for additional information.

In the AD pool of the initial period, the frequency of reported AEs within the SOC of psychiatric disorders was similar in the tralokinumab and placebo groups (Table 40).

**Table 40. AEs within the SOC Psychiatric Disorders by PT, Initial Treatment Period, AD Pool, Adjusted Pooling, Safety Analysis Set**

| System Organ Class (SOC) Preferred term (PT) | Tralokinumab (n=1605; PYE=473.19) | | | | Placebo (n=680; PYE=193.1) | | | |
|---|---|---|---|---|---|---|---|---|
| | N | (adj.%) | E | (adj.R) | N | (adj.%) | E | (adj.R) |
| Any AEs | 1080 | (65.7) | 3148 | 639.5 | 449 | (67.2) | 1276 | 678.3 |
| Psychiatric disorders | 53 | (3.1) | 61 | 12.7 | 20 | (2.9) | 21 | 11.0 |
| Insomnia | 24 | (1.4) | 26 | 5.2 | 9 | (1.3) | 9 | 4.6 |
| Anxiety | 9 | (0.5) | 10 | 1.9 | 5 | (0.7) | 5 | 2.5 |
| Depression | 6 | (0.4) | 6 | 1.3 | | | | |
| Sleep disorder | 7 | (0.4) | 7 | 1.3 | 2 | (0.3) | 2 | 1.1 |
| Depressed mood | 2 | (0.2) | 2 | 0.7 | 1 | (0.2) | 1 | 0.6 |
| Mood altered | 2 | (0.1) | 2 | 0.4 | | | | |
| Apathy | 1 | (0.1) | 1 | 0.5 | 1 | (0.2) | 2 | 1.1 |
| Restlessness | 1 | (0.1) | 2 | 0.5 | | | | |
| Panic attack | 1 | (0.1) | 1 | 0.2 | | | | |
| Agitation | 1 | (0.1) | 1 | 0.2 | | | | |
| Depression suicidal | 1 | (0.1) | 1 | 0.2 | | | | |
| Gambling disorder | 1 | (0.1) | 1 | 0.2 | | | | |
| Stress | 1 | (0.1) | 1 | 0.2 | | | | |
| Initial insomnia | | | | | 1 | (0.2) | 1 | 0.6 |
| Nicotine dependence | | | | | 1 | (0.2) | 1 | 0.6 |

AEs collected during the exposure time in the initial treatment period are shown
PYE: Patient years of exposure. N: Number of subjects with one or more events.
%: Percentage of subjects with one or more events. adj. %: Adjusted percentage calculated using CMH weights. E: Number of adverse events. R: Rate (number of events divided by patient-years of exposure multiplied by 100). adj. R: Adjusted rate calculated using CMH weights.

Source: BLA 761180, Module 2.7.4, Panel 75 (page 221).
Abbreviations: AD, atopic dermatitis; AE, adverse event; CMH, Cochran–Mantel–Haenszel; PT, preferred term; PYE, person-years of exposure; SOC, system organ class

In the AD pool, the frequency of reported AEs in the SOC of psychiatric disorders for the tralokinumab group was lower during the safety follow-up period (3.1/100 PYFU) compared to the initial period (12.7/100 PYE).

In the monotherapy pool, the frequency of reported AEs within the SOC of psychiatric disorders was similar in the tralokinumab (3.7%; 13.5/100 PYE) and placebo groups (3.0%; 11.4/100 PYE) during the initial period, and decreased in the tralokinumab Q2W group during the maintenance (5.9/100 PYE) and open-label (5.0/100 PYE) periods.

In ECZTRA-3, the frequency of reported AEs within the SOC of psychiatric disorders was similar in the tralokinumab+TCS (2.4%; 10.7/100 PYE) and placebo+TCS (2.4%; 7.9/100 PYE) groups during the initial period, and decreased in the tralokinumab Q2W+TCS group during the continuation period (5.7/100 PYE).

## Cardiovascular Adverse Events of Interest

The AEs of CV death, nonfatal myocardial infarction (MI), and nonfatal stroke were included as a safety area of interest at the request of the FDA but were not prospectively defined in the protocols or adjudicated by an external independent adjudication committee in the tralokinumab AD development program. The Applicant applied MedDRA searches for SMQs of MI (narrow scope) (MedDRA code 20000047) and central nervous system hemorrhages and cerebrovascular conditions (narrow scope) (MedDRA code 20000061). The Applicant also included fatal AEs with the most probable primary cause of death reported as CV death or unknown for the AD pool (all doses) and exposure pool (including trials in AD, asthma, idiopathic pulmonary fibrosis, and ulcerative colitis) for the entire duration of the trials (including the safety follow-up).

In the AD pool (all doses), the frequency of reported CV AEs of interest was similar in the tralokinumab group (0.4%; 0.5/100 PYO) and placebo group (0.3%; 0.9/100 PYO), including nonfatal stroke and nonfatal MI (Table 41).

**Table 41. Summary of Cardiovascular Events of Interest, AD Pool (All Doses), Entire Trial Period**

| | Tralokinumab total (n=2092; PYO = 1730.35) | | | | Placebo total (n=761; PYO = 316.59) | | | |
|---|---|---|---|---|---|---|---|---|
| | N | (%) | E | R | N | (%) | E | R |
| Any cardiovascular event of interest | 9 | (0.4) | 9 | 0.5 | 2 | (0.3) | 3 | 0.9 |
| Non-fatal cardiovascular events | 8 | (0.4) | 8 | 0.5 | 2 | (0.3) | 3 | 0.9 |
| Non-fatal stroke (SMQ) | 3 | (0.1) | 3 | 0.2 | 1 | (0.1) | 1 | 0.3 |
| Non-fatal MI (SMQ) | 5 | (0.2) | 5 | 0.3 | 1 | (0.1) | 2 | 0.6 |
| Fatal cardiovascular events[a] | 1 | (<0.1) | 1 | 0.1 | 0 | (0.0) | 0 | 0.0 |
| Unknown | 1 | (<0.1) | 1 | 0.1 | 0 | (0.0) | 0 | 0.0 |

**Abbreviations:** E = number of adverse events; n = number of subjects; N = number of subjects with one or more events; PYO = patient years of observation; R = rate (number of events divided by patient-years of observation multiplied by 100); % = percentage of subjects with one or more events

**Notes:** a = In addition, 1 subject treated with tralokinumab in ECZTRA 1 died from an MI approximately 8 months after the last dose of IMP. The event was reported after lock of the clinical database and is not included in the statistical output.

Source: BLA 761180, Module 2.7.4, Panel 77 (page 224).
Abbreviations: AD, atopic dermatitis; ECZTRA, ECZema TRAlokinumab; IMP, investigational medicinal product; MI, myocardial infarction; SMQ, standardized Medical Dictionary for Regulatory Activities query

Refer to Section 7.6.1 for details on the CV death (Subject [redacted](b) (6)) and non-CV death (Subject ECZTRA-5[redacted](b) (6), primary cause of death was reported as septic shock and respiratory failure).

In the exposure pool (all indications), the frequency of reported CV AEs of interest was similar in the tralokinumab group (0.7%; 0.8/100 PYO) and placebo group (0.8%; 0.9/100 PYO), including CV (or unknown cause of) death (tralokinumab group [0.2%; 0.2/100 PYO] and placebo group [0.1%; 0.2/100 PYO]), nonfatal stroke (tralokinumab group [0.3%; 0.4/100 PYO] and placebo group [0.4%; 0.4/100 PYO]), and nonfatal MI (tralokinumab group [0.2%; 0.2/100 PYO] and placebo group [0.2%; 0.3/100 PYO]).

## Rare Adverse Events

The Applicant conducted a MedDRA search for a list of PTs for rare events issued by the European Medicines Agency in 2016.

In the AD pool (all doses) during the entire trial period, the frequency of reported rare AEs was similar in the tralokinumab group (1.4/100 PYO) and placebo group (1.3/100 PYO) (Table 42).

**Table 42. Summary of Rare Events by SOC and PT, Entire Trial Period, AD Pool (All Doses), Safety Analysis Set**

| System organ class (SOC) Preferred term (PT) | Tralokinumab Total (n=2092, PYO=1730.35) N | (%) | E | R | Placebo Total (n=761, PYO=316.59) N | (%) | E | R |
|---|---|---|---|---|---|---|---|---|
| Any AEs | 19 | (0.9) | 25 | 1.4 | 4 | (0.5) | 4 | 1.3 |
| Skin and subcutaneous tissue disorders | 11 | (0.5) | 17 | 1.0 | 3 | (0.4) | 3 | 0.9 |
| Angioedema | 6 | (0.3) | 8 | 0.5 | 2 | (0.3) | 2 | 0.6 |
| Dermatitis exfoliative generalised | 4 | (0.2) | 4 | 0.2 | 1 | (0.1) | 1 | 0.3 |
| Dermatitis exfoliative | 3 | (0.1) | 5 | 0.3 | | | | |
| Immune system disorders | 4 | (0.2) | 4 | 0.2 | | | | |
| Anaphylactic reaction | 4 | (0.2) | 4 | 0.2 | | | | |
| Renal and urinary disorders | 2 | (0.1) | 2 | 0.1 | 1 | (0.1) | 1 | 0.3 |
| Acute kidney injury | 2 | (0.1) | 2 | 0.1 | 1 | (0.1) | 1 | 0.3 |
| Ear and labyrinth disorders | 1 | (<0.1) | 1 | 0.1 | | | | |
| Deafness | 1 | (<0.1) | 1 | 0.1 | | | | |
| Hepatobiliary disorders | 1 | (<0.1) | 1 | 0.1 | | | | |
| Acute hepatic failure | 1 | (<0.1) | 1 | 0.1 | | | | |

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 observation multiplied by 100). Classification according to MedDRA 20.0. PYO: Patient years of observation.

Source: BLA 761180, Module 2.7.4, Panel 79, page 228.
Abbreviations: AD, atopic dermatitis; AE, adverse event

In the exposure pool for the entire trial period, the frequency of reported rare AEs was similar in the tralokinumab group (0.9/100 PYO) and placebo group (0.9/100 PYO), with no clinically relevant differences reported between the tralokinumab and placebo groups across the types of rare AEs included in the search.

# Laboratory Findings, AD Pool (ECZTRA-1, -2, -3, -5), Initial Period; Monotherapy (ECZTRA-1, -2), Initial/Maintenance Periods

## Chemistry

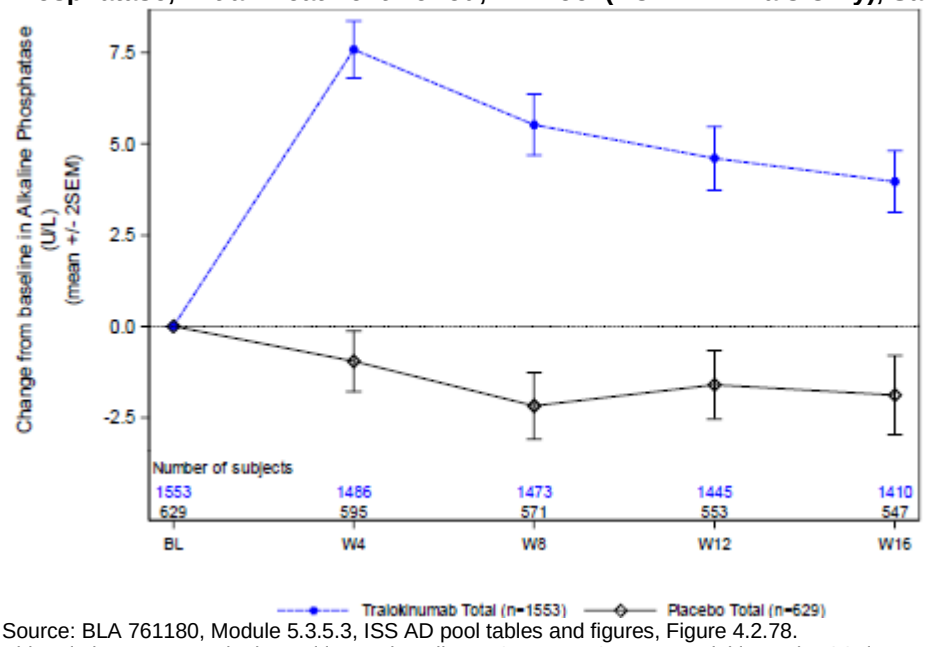
The chemistry parameters assessed included electrolytes (sodium, potassium, calcium), renal function parameters (creatinine, urea nitrogen, albumin, protein), liver enzymes, lipids (cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides), glucose (nonfasting), and biomarkers (lactate dehydrogenase [LDH], IgE).

No clinically significant mean changes were reported from baseline to the end of the treatment period for the chemistry parameters in the AD pool (ECZTRA trials, initial period), the monotherapy pool (initial, maintenance and open-label periods), or ECZTRA-3 (initial and continuation periods).

## Liver Parameters

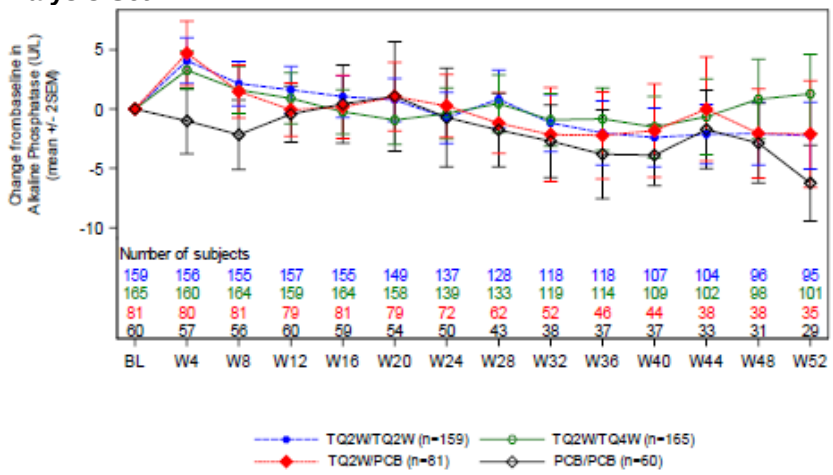
The mean values of liver enzymes (alanine phosphatase, alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin [BILI], and gamma-glutamyl transferase) remained within the normal ranges (with minor fluctuations). The mean alkaline phosphatase level remained stable in the placebo group, but increased from baseline to Week 4 in the tralokinumab group, with a trend towards return to baseline (Figure 10 and Figure 11).

**Figure 10. Mean Change From Baseline in Biochemistry Parameters Over Time, Alkaline Phosphatase, Initial Treatment Period, AD Pool (ECZTRA Trials Only), Safety Analysis Set**




Source: BLA 761180, Module 5.3.5.3, ISS AD pool tables and figures, Figure 4.2.78.
Abbreviations: AD, atopic dermatitis; BL, baseline; ECZTRA, ECZema TRAlokinumab; ISS, integrated summary of safety; SEM, standard error of the mean; W, week

**Figure 11. Mean Change From Baseline in Biochemistry Parameters Over Time, Alkaline Phosphatase, Initial and Maintenance Treatment Periods, Monotherapy Pool, Maintenance Safety Analysis Set**




BL: Baseline. SEM: Standard error of the mean. W: Week.
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.

Source: BLA 761180, Module 5.3.5.3 ISS monotherapy pool tables and figures, Figure 4.4.186.
Abbreviations: AD, atopic dermatitis; ISS, integrated summary of safety

## Drug-Induced Liver Injury

No subject in the AD pool was reported to have a TEAE of drug-induced liver injury (DILI).

In the asthma pool, one subject in the tralokinumab group was reported to have a nonserious TEAE of DILI attributed to concomitant treatment with norfloxacin and flavoxate hydrochloride for cystitis. This TEAE was deemed not related to tralokinumab, and the outcome was reported as resolved.

## Concurrent Elevations of ALT or AST ≥3× and BILI ≥2× Upper Limit of Normal

In all tralokinumab clinical trials, a total of four subjects had concurrent elevations of ALT or AST ≥3× upper limit of normal (ULN) and BILI ≥2× ULN (including two subjects in the asthma trial, STRATOS2, and two subjects in the AD trial, ECZTRA-1). None was attributed to tralokinumab.

In the asthma trial, alternative etiologies to explain liver parameter elevations included high intake of alcohol and pain medications for a subject in the tralokinumab group, and acute hepatitis A for one subject in the placebo group.

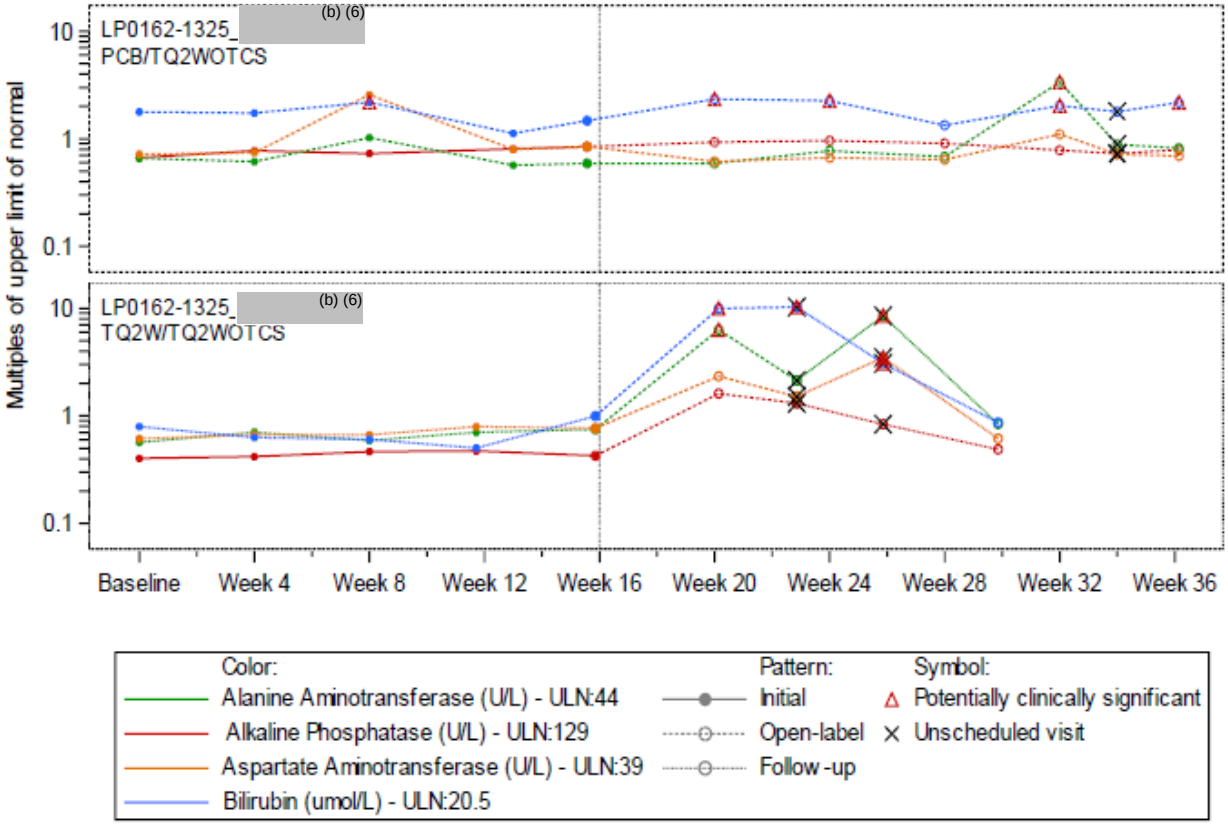
In the AD trial ECZTRA-1, Subjects (b) (6) and (b) (6) had the following alternative etiologies for their concurrent elevations in liver parameters (Figure 12; also refer to the graph in Module 2.7.4, Panel 94):

- Subject (b) (6) (a 20-year-old male) was discontinued from the trial in the open-label period. The Investigator considered this TEAE as *probably related* to the study drug, with the outcome reported as recovered/resolved. Alternative etiologies for this TEAE included concomitant medications (levocetirizine and ibuprofen). The subject had

elevated bilirubin levels at baseline and during the trial, and a TEAE of hepatic enzyme increase was reported during the initial treatment period with placebo.

- Subject (b) (6) (a 31-year-old male) discontinued the trial in the open-label period for this SAE. The subject had a family history of cholecystitis and reported epigastric pain with radiation and jaundice. The Investigator considered this SAE as possibly related to the study drug. However, after a review by an external consultant hepatologist, the etiology was determined as transient bile duct obstruction from a gallstone. The Applicant changed its causality to *not related*. The outcome of this SAE was reported as recovered/resolved.

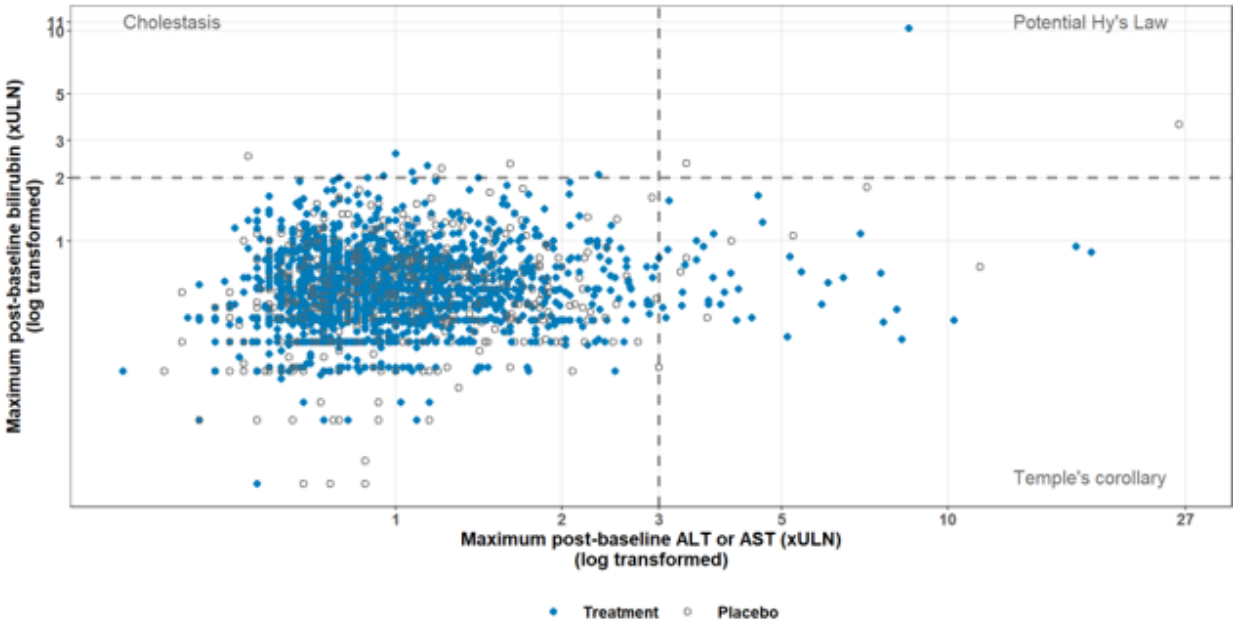
**Figure 12. Individual AST, ALT, and BILI in Subjects With Concurrent Elevations of ALT or AST ≥3× ULN and BILI ≥2× ULN—ECZTRA-1**




PCB/TQ2WOTCS = Placebo - Tralokinumab every two weeks + Optional topical corticosteroid.
TQ2W/TQ2WOTCS = Tralokinumab every two weeks - Tralokinumab every two weeks + Optional topical corticosteroid.
Source: BLA 761180, Module 2.7.4, Panel 94 (page 268).
Abbreviations: Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BILI, bilirubin; ECZTRA, ECZema TRAlokinumab; ULN, upper limit of normal

Figure 13 presents the DILI case screening plot for the AD pool for the entire treatment period.

**Figure 13. DILI Case Screening Plot, Safety Population, AD Pool (ECZTRA Trials Only) During the Entire Treatment Period**




Source: adlb.xpt
Software: R
ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI= total bilirubin; ULN = upper limit of normal; ALP= alkaline phosphatase
Each data point represents at least one visit (from a subject) with both ALT/AST and TB values in post-baseline period. A potential Hy's Law Case was classified as if maximum post-baseline TB exceeds 2*ULN within any days after maximum post-baseline ALT or AST exceeds 3*ULN, without findings of cholestasis (defined as ALP<2*ULN).

Source: Clinical data safety reviewer for BLA 761180.
Abbreviations: AD, atopic dermatitis; DILI, drug-induced liver injury; ECZTRA, ECZema TRAlokinumab

## Hematology

No clinically significant mean changes from baseline to the end of the treatment periods were reported for red blood cells (erythrocytes, hematocrit, hemoglobin, erythrocyte mean corpuscular hemoglobin concentration, and erythrocyte mean corpuscular volume), platelets, or white blood cells (basophils, basophils/leukocytes, lymphocytes, lymphocytes/leukocytes, monocytes, monocytes/leukocytes, neutrophils, neutrophils/leukocytes, and leukocytes) in the AD pool (initial period, ECZTRA trials), the monotherapy pool (initial, maintenance, and open-label periods), or ECZTRA-3 (initial period).

The proportion of subjects with potentially clinically significant values (PCSV) for hematology parameters during the initial treatment period in the AD pool (ECZTRA trials) were similar in the tralokinumab and placebo groups. The most commonly reported PCSVs were monocytes $>0.8\times10^9$ /L (25.6% for the tralokinumab group, 25.3% for the placebo group) and lymphocytes between 0.5 and $1.0\times10^9$ /L (8.4% for tralokinumab group, 11.3% for placebo group). A similar pattern was observed for the monotherapy pool and ECZTRA-3.

Table 43 summarizes the PCSVs of hematologic parameters for the initial period of the AD pool (ECZTRA trials).

**Table 43. Summary of Subjects With Potentially Clinically Significant Hematology Values, Initial Treatment Period, AD Pool (ECZTRA Trials Only), Safety Analysis Set**

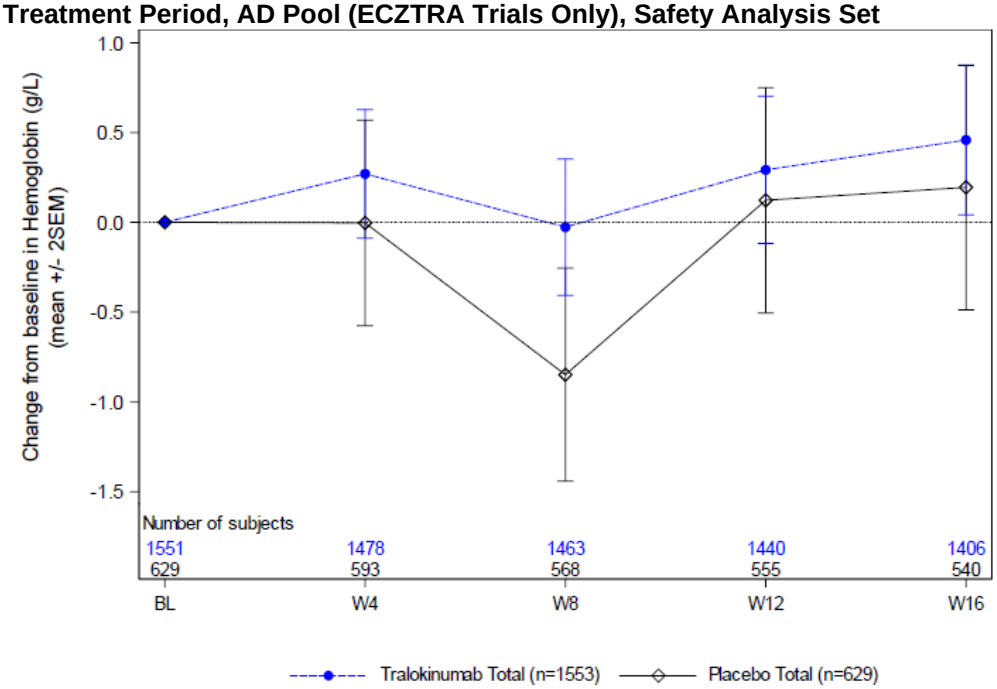
| | Tralokinumab Total (n=1553) N (%) | Placebo Total (n=629) N (%) |
|---|---|---|
| Hemoglobin (g/L) | | |
| Hemoglobin < 80 g/L | 1 ( 0.1) | |
| 80 g/L <= Hemoglobin < 110 g/L | 34 ( 2.2) | 20 ( 3.2) |
| Hemoglobin > 165 g/L (Female) / 185 g/L (Male) | 6 ( 0.4) | 6 ( 1.0) |
| Basophils (10^9/L) | | |
| Basophils > 0.2 (10^9/L) | 9 ( 0.6) | 3 ( 0.5) |
| Eosinophils (10^9/L) | | |
| 1.5 (10^9/L) < Eosinophils <= 5.0 (10^9/L) | 346 ( 22.3) | 59 ( 9.4) |
| Eosinophils > 5.0 (10^9/L) | 19 ( 1.2) | 2 ( 0.3) |
| Lymphocytes (10^9/L) | | |
| Lymphocytes < 0.5 (10^9/L) | 6 ( 0.4) | 3 ( 0.5) |
| 0.5 (10^9/L) <= Lymphocytes < 1.0 (10^9/L) | 130 ( 8.4) | 71 ( 11.3) |
| Lymphocytes > 5.0 (10^9/L) | 4 ( 0.3) | 1 ( 0.2) |
| Monocytes (10^9/L) | | |
| Monocytes < 0.1 (10^9/L) | 4 ( 0.3) | |
| Monocytes > 0.8 (10^9/L) | 398 ( 25.6) | 159 ( 25.3) |
| Neutrophils (10^9/L) | | |
| Neutrophils < 0.5 (10^9/L) | 1 ( 0.1) | |
| 0.5 (10^9/L) <= Neutrophils < 1.0 (10^9/L) | 5 ( 0.3) | 3 ( 0.5) |
| 1.0 (10^9/L) <= Neutrophils < 1.5 (10^9/L) | 28 ( 1.8) | 9 ( 1.4) |
| Platelets (10^9/L) | | |
| Platelets < 10 (10^9/L) | | |
| 10 (10^9/L) <= Platelets < 30 (10^9/L) | | |
| 30 (10^9/L) <= Platelets < 100 (10^9/L) | 1 ( 0.1) | 1 ( 0.2) |
| Platelets > 450 (10^9/L) | 55 ( 3.5) | 28 ( 4.5) |

Source: BLA 761180, Module 5.3.5.3, Integrated Summary of Safety atopic dermatitis pool tables and figures, Table 4.1.15.

Figure 14 to Figure 25 depict the mean changes from baseline for the initial period in the AD pool (ECZTRA-1, -2, -3, and -5), and the initial/maintenance periods in the monotherapy trials (ECZTRA-1 and -2), respectively, for each parameter.

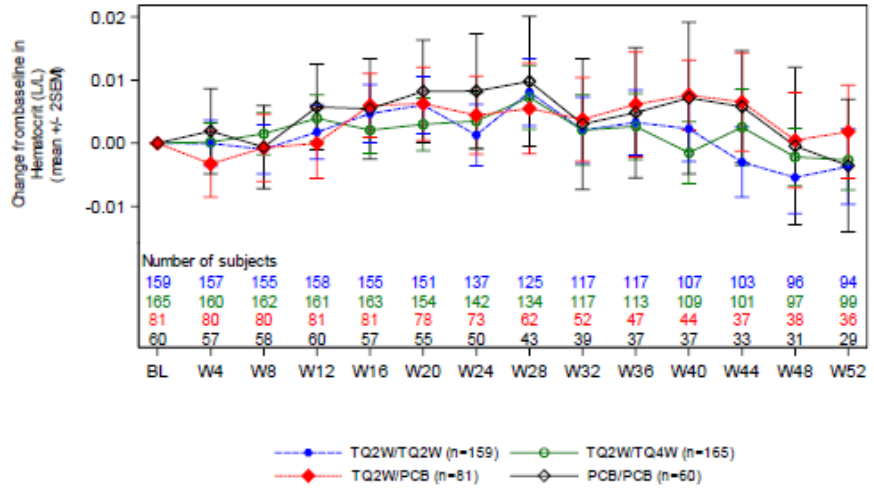
## Hemoglobin

**Figure 14. Mean Change From Baseline in Hematology Parameters Over Time, Hemoglobin, Initial Treatment Period, AD Pool (ECZTRA Trials Only), Safety Analysis Set**




Source: BLA 761180, Module 5.3.5.3, ISS AD pool tables and figures, Figure 4.2.94.
Abbreviations: AD, atopic dermatitis; BL, baseline; ECZTRA, ECZema TRAlokinumab; ISS, integrated summary of safety; W, week; SEM, standard error of the mean

**Figure 15. Mean Change From Baseline in Hematology Parameters Over Time, Hematocrit, Initial and Maintenance Treatment Periods, Monotherapy Pool, Maintenance Safety Analysis Set**



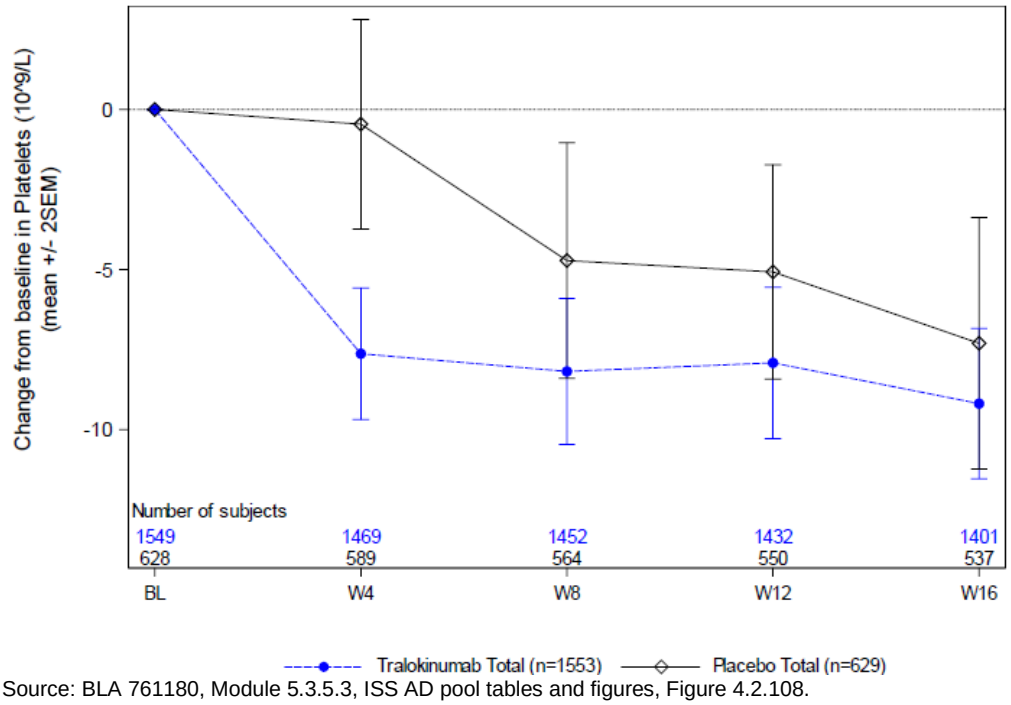

BL: Baseline. SEM: Standard error of the mean. W: Week.
TQ2W/TQ2W: Week 16 Tralokinumab responder - Tralokinumab every two weeks.
TQ2W/TQ4W: Week 16 Tralokinumab responder - Tralokinumab every four weeks.
TQ2W/PCB: Week 16 Tralokinumab responder - Placebo.
PCB/PCB: Week 16 Placebo responder - Placebo.

Source: BLA 761180, Module 5.3.5.3 Integrated Summary of Safety monotherapy pool tables and figures, Figure 4.4.201

The PT of anemia (mild/possibly related/dose not changed/resolved) was reported for one subject (ECZTRA [redacted] (b) (6)) in the tralokinumab group for the initial period.

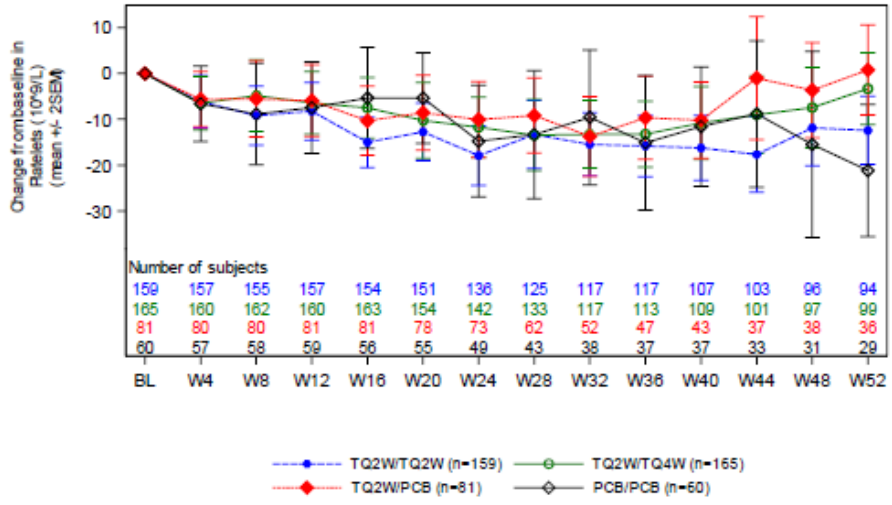
## Platelets

**Figure 16. Mean Change From Baseline in Hematology Parameters Over Time, Platelets, Initial Treatment Period, AD Pool (ECZTRA Trials Only), Safety Analysis Set**




Source: BLA 761180, Module 5.3.5.3, ISS AD pool tables and figures, Figure 4.2.108.
Abbreviations: AD, atopic dermatitis; BL, baseline; ECZTRA, ECZema TRAlokinumab; ISS, integrated summary of safety; W, week; SEM, standard error of the mean

**Figure 17. Mean Change from Baseline in Hematology Parameters Over Time, Platelets, Initial and Maintenance Treatment Periods, Monotherapy Pool, Maintenance Safety Analysis Set**

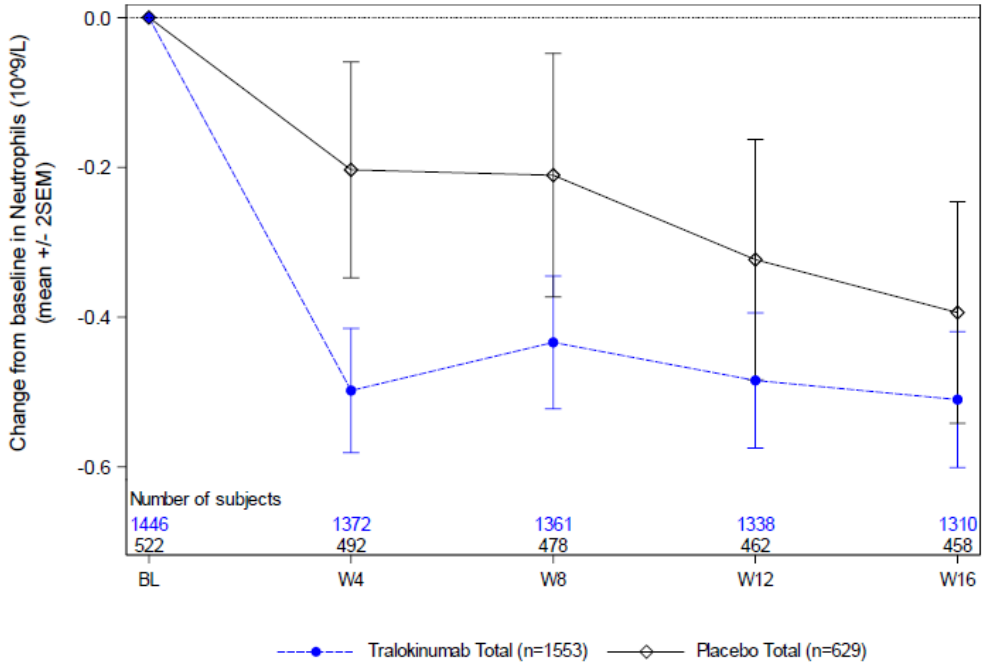



BL: Baseline. SEM: Standard error of the mean. W: Week.
TQ2W/TQ2W: Week 16 Tralokinumab responder - Tralokinumab every two weeks.
TQ2W/TQ4W: Week 16 Tralokinumab responder - Tralokinumab every four weeks.
TQ2W/PCB: Week 16 Tralokinumab responder - Placebo.
PCB/PCB: Week 16 Placebo responder - Placebo.
Source: BLA 761180, Module 5.3.5.3 Integrated Summary of Safety monotherapy pool tables and figures, Figure 4.4.216.

No subject was reported with the PT of thrombocytopenia or platelet count decreased in the tralokinumab group for the initial period.

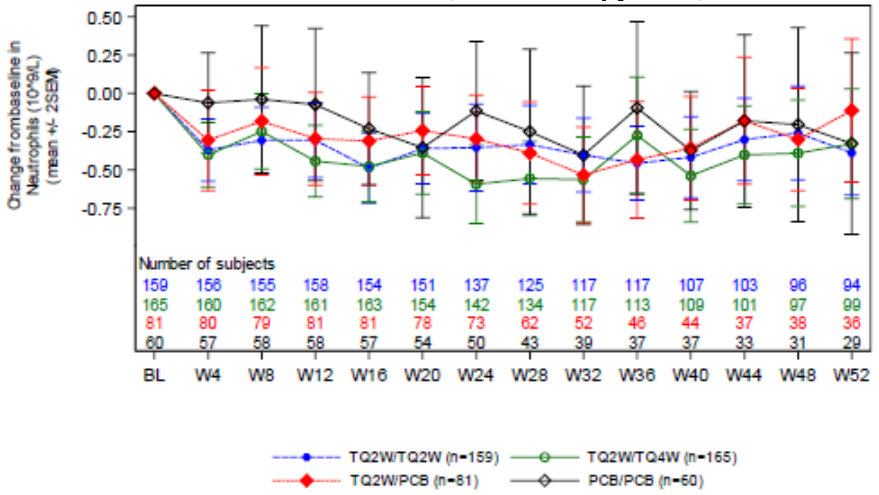
## Neutrophils

**Figure 18. Mean Change From Baseline in Hematology Parameters Over Time, Neutrophils, Initial Treatment Period, AD Pool (ECZTRA Trials Only), Safety Analysis Set**




Source: BLA 761180, Module 5.3.5.3, ISS AD pool tables and figures, Figure 4.2.98.
Abbreviations: AD, atopic dermatitis; BL, baseline; ECZTRA, ECZema TRAlokinumab; ISS, integrated summary of safety; W, week; SEM, standard error of the mean

**Figure 19. Mean Change From Baseline in Hematology Parameters Over Time, Neutrophils, Initial and Maintenance Treatment Periods, Monotherapy Pool, Maintenance Safety Analysis Set**



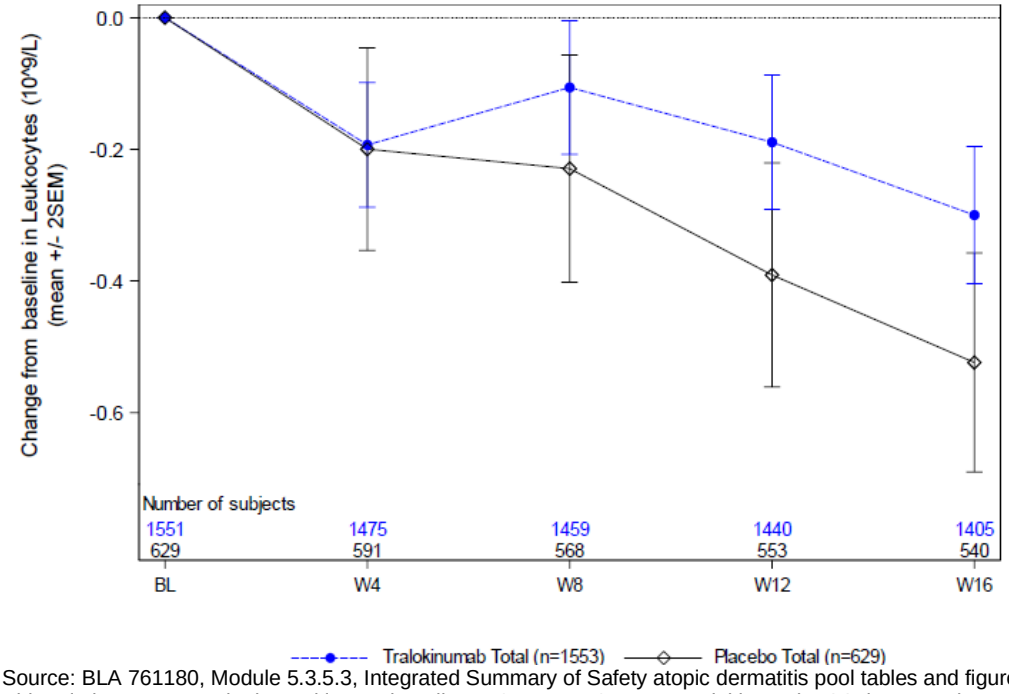

BL: Baseline. SEM: Standard error of the mean. W: Week.
TQ2W/TQ2W: Week 16 Tralokinumab responder - Tralokinumab every two weeks.
TQ2W/TQ4W: Week 16 Tralokinumab responder - Tralokinumab every four weeks.
TQ2W/PCB: Week 16 Tralokinumab responder - Placebo.
PCB/PCB: Week 16 Placebo responder - Placebo.

Source: BLA 761180, Module 5.3.5.3 Integrated Summary of Safety monotherapy pool tables and figures, Figure 4.4.206.

The PT of neutropenia/neutrophil count decreased (moderate/possibly related/drug interrupted/resolved) was reported for one subject (ECZTRA-[redacted] (b) (6)) in the tralokinumab group for the initial period.

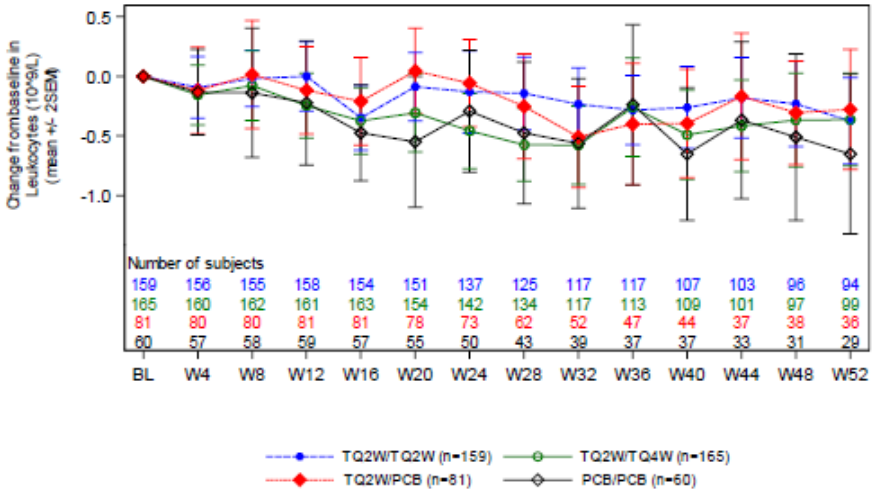
## Leukocytes

**Figure 20. Mean Change From Baseline in Hematology Parameters Over Time, Leukocytes, Initial Treatment Period, AD Pool (ECZTRA Trials Only), Safety Analysis Set**




Source: BLA 761180, Module 5.3.5.3, Integrated Summary of Safety atopic dermatitis pool tables and figures, Figure 4.2.97.
Abbreviations: AD, atopic dermatitis; BL, baseline; ECZTRA, ECZema TRAlokinumab; ISS, integrated summary of safety; W, week; SEM, standard error of the mean

**Figure 21. Mean Change From Baseline in Hematology Parameters Over Time, Leukocytes, Initial and Maintenance Treatment Periods, Monotherapy Pool, Maintenance Safety Analysis Set**



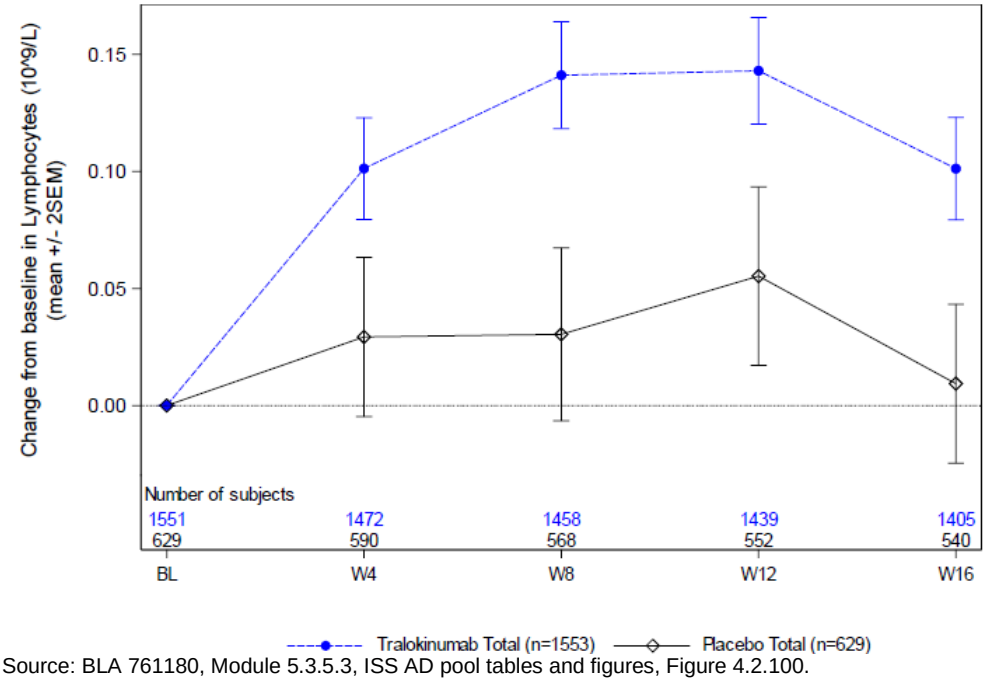

BL: Baseline. SEM: Standard error of the mean. W: Week.
TQ2W/TQ2W: Week 16 Tralokinumab responder - Tralokinumab every two weeks.
TQ2W/TQ4W: Week 16 Tralokinumab responder - Tralokinumab every four weeks.
TQ2W/PCB: Week 16 Tralokinumab responder - Placebo.
PCB/PCB: Week 16 Placebo responder - Placebo.

Source: BLA 761180, Module 5.3.5.3 Integrated Summary of Safety monotherapy pool tables and figures, Figure 4.4.205.

The PT of leukopenia was reported for no subject in the tralokinumab group and one subject in the placebo group for the initial period.

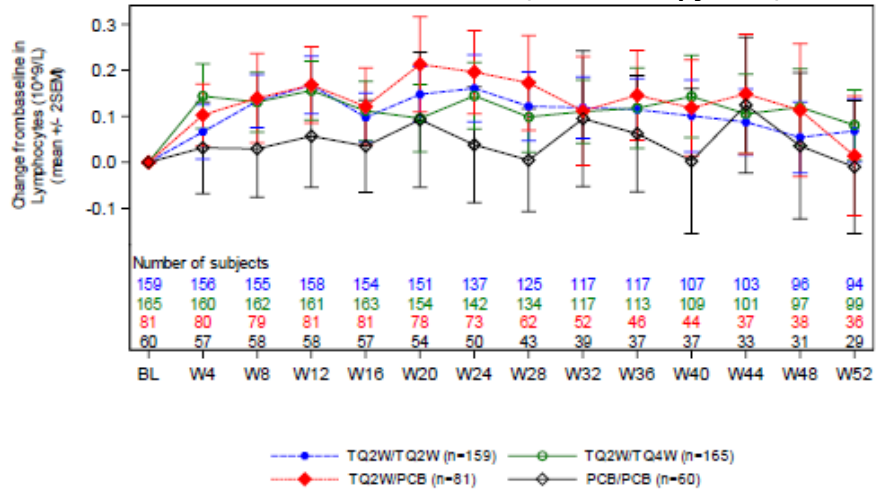
## Lymphocytes

**Figure 22. Mean Change From Baseline in Hematology Parameters Over Time, Lymphocytes, Initial Treatment Period, AD Pool (ECZTRA Trials Only), Safety Analysis Set**




Source: BLA 761180, Module 5.3.5.3, ISS AD pool tables and figures, Figure 4.2.100.
Abbreviations: AD, atopic dermatitis; BL, baseline; ECZTRA, ECZema TRAlokinumab; ISS, integrated summary of safety; W, week; SEM, standard error of the mean

**Figure 23. Mean Change From Baseline in Hematology Parameters Over Time, Lymphocytes, Initial and Maintenance Treatment Periods, Monotherapy Pool, Maintenance Safety Analysis Set**

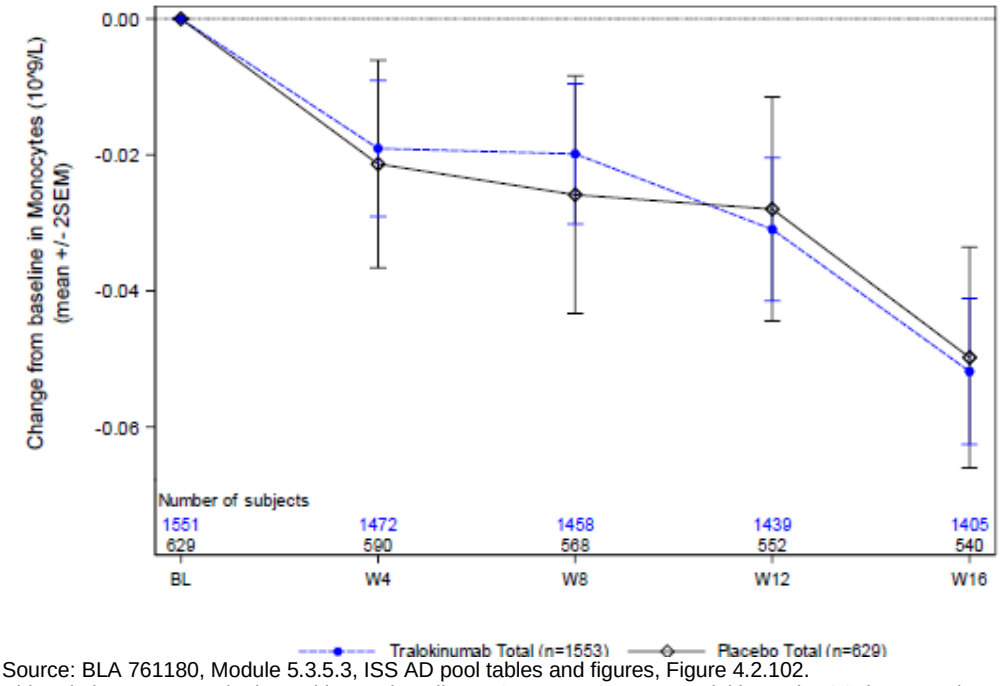



BL: Baseline. SEM: Standard error of the mean. W: Week.
TQ2W/TQ2W: Week 16 Tralokinumab responder - Tralokinumab every two weeks.
TQ2W/TQ4W: Week 16 Tralokinumab responder - Tralokinumab every four weeks.
TQ2W/PCB: Week 16 Tralokinumab responder - Placebo.
PCB/PCB: Week 16 Placebo responder - Placebo.

Source: BLA 761180, Module 5.3.5.3 Integrated Summary of Safety monotherapy pool tables and figures, Figure 4.4.208.

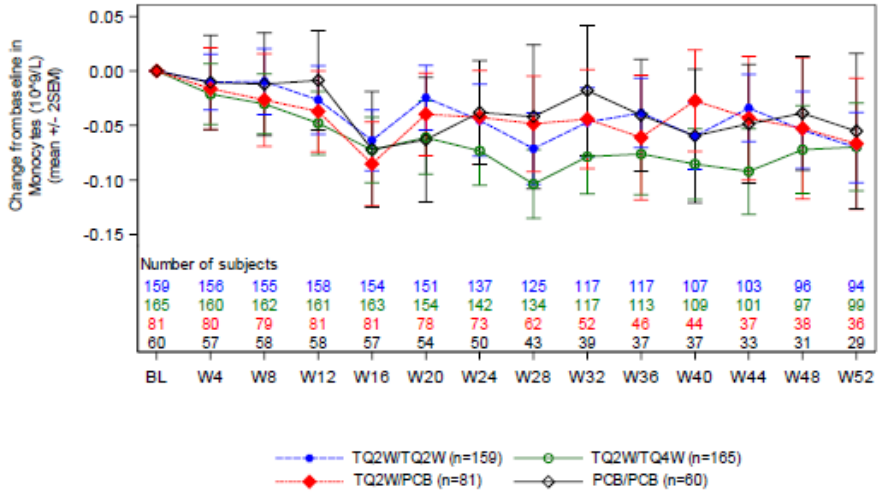
## Monocytes

**Figure 24. Mean Change From Baseline in Hematology Parameters Over Time, Monocytes, Initial Treatment Period, AD Pool (ECZTRA Trials Only), Safety Analysis Set**




Source: BLA 761180, Module 5.3.5.3, ISS AD pool tables and figures, Figure 4.2.102.
Abbreviations: AD, atopic dermatitis; BL, baseline; ECZTRA, ECZema TRAlokinumab; ISS, integrated summary of safety; W, week; SEM, standard error of the mean

**Figure 25. Mean Change From Baseline in Hematology Parameters Over Time, Monocytes, Initial and Maintenance Treatment Periods, Monotherapy Pool, Maintenance Safety Analysis Set**




BL: Baseline. SEM: Standard error of the mean. W: Week.
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.

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Source: BLA 761180, Module 5.3.5.3 Integrated Summary of Safety monotherapy pool tables and figures, Figure 4.4.210.

## Eosinophils

The baseline mean values of eosinophils were elevated (>ULN $0.5\times10^9$/L) in the tralokinumab (44.5%) and placebo (41.8%) treatment groups in a similar proportion of subjects (Table 44).

PCSV for eosinophil count (>$1.5\times10^9$/L) at baseline was reported for a similar proportion of subjects in the tralokinumab group (7.7%) compared to the placebo group (7.2%), and for a greater proportion of subjects in the tralokinumab group compared to the placebo group during the initial treatment period (with a decline towards baseline at the end of the initial treatment period). A similar trend was reported during the maintenance period.

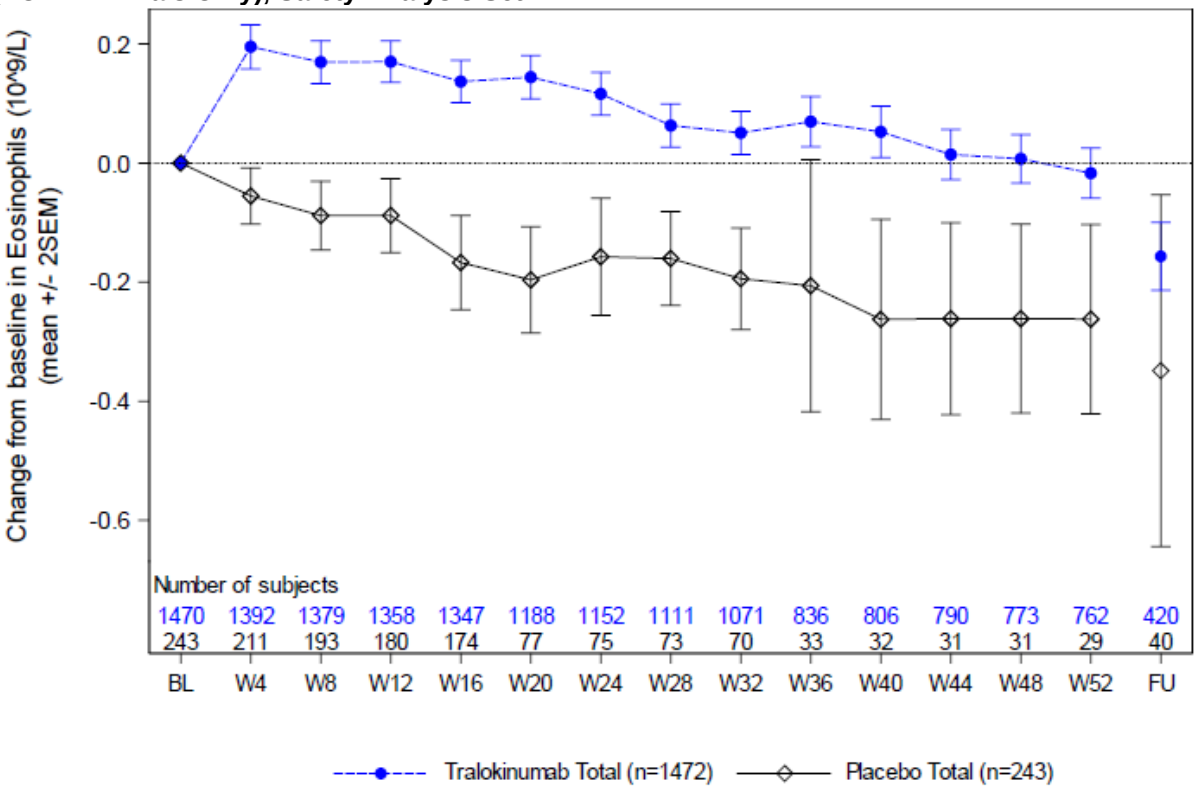
**Table 44. Summary of Subjects With PCSVs for Eosinophil Count, Initial Treatment Period, AD Pool (ECZTRA Trials Only), Safety Analysis Set**

| | Tralokinumab Total (n=1553) N (%) | Placebo Total (n=629) N (%) |
|---|---|---|
| During the initial treatment period | | |
| Eosinophils (10^9/L) | | |
| 1.5 (10^9/L) < Eosinophils <=5.0 (10^9/L) | 346 ( 22.3) | 59 ( 9.4) |
| Eosinophils >5.0 (10^9/L) | 19 ( 1.2) | 2 ( 0.3) |
| At the end of the initial treatment period | | |
| Eosinophils (10^9/L) | | |
| 1.5 (10^9/L) < Eosinophils <=5.0 (10^9/L) | 192 ( 12.4) | 28 ( 4.5) |
| Eosinophils >5.0 (10^9/L) | 7 ( 0.5) | 1 ( 0.2) |

Source: BLA 761180, Module 2.7.4, Panel 99.
Abbreviations: AD, atopic dermatitis; ECZTRA, ECZema TRAlokinumab; PCSV, potentially clinically significant value

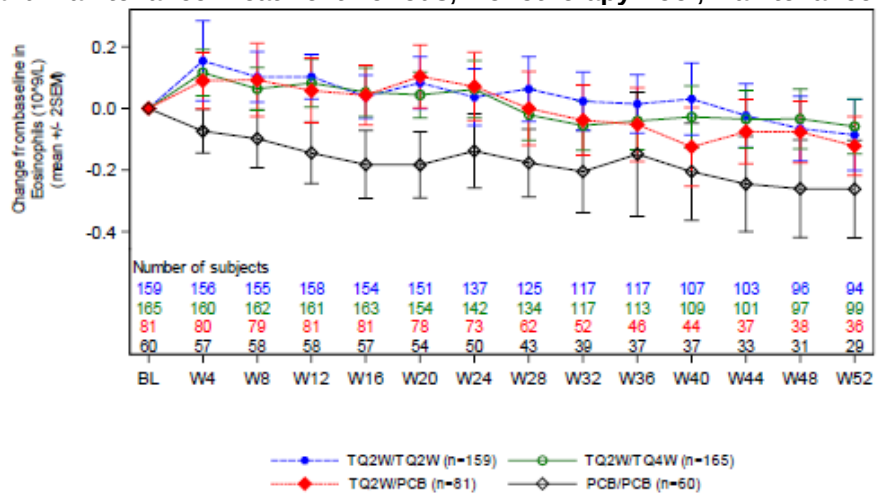
A transient increase in mean eosinophil value was reported for the tralokinumab groups in the AD pool (ECZTRA trials), the monotherapy pool, and ECZTRA-3, with a decline to less than their baseline values for all treatment groups at Week 52 (Figure 26 and Figure 27).

**Figure 26. Mean Change From Baseline in Eosinophils Over Time, Entire Trial Period, AD Pool (ECZTRA Trials Only), Safety Analysis Set**




BL: Baseline. FU: Safety follow-up. SEM: Standard error of the mean. W: Week. Subjects on tralokinumab or placebo throughout the trial were included. Subjects switching IMP during the trial were excluded.
Source: BLA 761180, Module 5.3.5.3, ISS AD pool tables and figures; and Module 2.7.4, Panel 97.
Abbreviations: AD, atopic dermatitis; ECZTRA, ECZema TRAlokinumab; IMP, investigational medicinal product

**Figure 27. Mean Change From Baseline of Hematology Parameters Over Time, Eosinophils, Initial and Maintenance Treatment Periods, Monotherapy Pool, Maintenance Safety Analysis Set**




BL: Baseline. SEM: Standard error of the mean. W: Week.
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.
Source: BLA 761180, Module 5.3.5.3 Integrated Summary of Safety monotherapy pool tables and figures, Figure 4.4.212.

TEAEs of eosinophilia (PTs of eosinophil count increased and eosinophilia) were reported in a higher proportion of subjects in tralokinumab groups compared with the placebo groups (PT of eosinophil count increased [0.5% versus 0] and PT of eosinophilia [0.9% versus 0.3%]). Most subjects had elevated eosinophil values at baseline. Two subjects in the ECZTRA-1 Trial (28317, 28302) experienced AD flare-ups and were reported with SAEs of eosinophilia (refer to the SAE narratives in Section III.17 for details).

The shifts in eosinophil values from normal ($<0.5\times10^9$/L) to potentially clinically significant values ($>1.5\times10^9$/L) were transient for both treatment groups.

**Vital Signs**

No clinically significant changes in the vital signs (diastolic blood pressure, systolic blood pressure, heart rate) were observed in any treatment group during the initial treatment period in the AD pool, the maintenance or open-label treatment period of the monotherapy pool, or the initial or continuation treatment period in the ECZTRA-3 trial.

The TEAE of hypertension related to vital signs was reported at a similar frequency in subjects in the tralokinumab and placebo groups (1.4% versus 1.1%) in the AD pool. The frequency of TEAEs related to vital signs was low and similar in the tralokinumab and placebo groups for the duration of the monotherapy and ECZTRA-3 trials.

**Thorough QT Study and ECG**

The Applicant proposed, and the Agency accepted, a plan not to conduct a thorough QT/corrected QT study for tralokinumab, because monoclonal antibodies are not expected to interact with ion channels due to their large molecular size and weight, and high specificity.

A blinded external expert conducted routine 12-lead ECG monitoring in all ECZTRA trials. Abnormal ECG findings considered clinically significant by the Investigator were recorded as AEs.

No clinically significant changes were observed in any treatment groups during the initial treatment period in the AD pool, during the initial/maintenance/open-label treatment periods in the monotherapy pool, or the initial/maintenance treatment periods of ECZTRA-3.

# 8. Therapeutic Individualization

## 8.1. Intrinsic Factors

No clinically significant differences in the PK of tralokinumab-ldrm were observed based on age (range 18 to 92 years), sex, mild-to-moderate renal impairment, or mild hepatic impairment. The effect of severe renal impairment or moderate-to-severe hepatic impairment on the pharmacokinetics of tralokinumab-ldrm is unknown.

## 8.2. Drug Interactions

See Section III.14 for this discussion.

## 8.3. Plans for Pediatric Drug Development

An adequate ePPND study in cynomolgus monkeys was conducted with tralokinumab to evaluate the potential toxicity in juvenile animals. No treatment-related effects in juvenile animals were noted in this ePPND study. The results from this ePPND study support treatment of pediatric subjects with tralokinumab. Refer to Section III.13 for details.

The initial approval of tralokinumab for treatment of moderate-to-severe AD in subjects (b) (4) will be limited to adult subjects (pediatric subjects were not included in the Phase 3 trials).

The product triggers the Pediatric Research Equity Act as a new active ingredient. Therefore, Pediatric Research Equity Act postmarketing requirements will be issued at the time of BLA licensing, to include the following four studies:

(1) LP0162-1334: Efficacy and safety (Phase 3, randomized, double-blind, placebo-controlled, parallel-group, monotherapy trial) in adolescents (12 to <18 years of age) with moderate-to-severe AD who are candidates for systemic AD treatment.
(2) LP0162-1335: PK and safety (Phase 1, randomized, single [observer] blinded, parallel-group, monotherapy trial) in pediatric subjects (2 to <12 years of age) with severe AD who are candidates for systemic AD treatment (studied sequentially in two cohorts: 6 to <12 years and 2 to <6 years).
(3) LP0162-1336: Efficacy and safety (Phase 3, randomized, double-blind, placebo-controlled, parallel-group trial with tralokinumab and placebo in combination with TCS therapy) in pediatric subjects (2 to <12 years of age) with severe AD who are candidates for systemic AD treatment (studied simultaneously in two cohorts: 6 to <12 years and 2 to <6 years).
(4) LP0162-1381: Efficacy, safety, and PK (Phase 2, single-arm, open-label, monotherapy trial) in infants and pediatric subjects (6 months to <2 years of age) with severe AD who are candidates for systemic AD treatment.

(b) (4)

## 8.4. Pregnancy and Lactation

### 8.4.1. Animal Data

The following nonclinical information was used in support of product labeling. Refer to Section III.13 for details.

In a pilot embryofetal development study, doses of up to 100 mg/kg tralokinumab were administered IV to pregnant cynomolgus monkeys once every week during organogenesis. No maternal or embryofetal toxicity was observed at doses up to 100 mg/kg/week tralokinumab (10 times the maximum recommended human dose [MRHD] on a mg/kg basis of 10 mg/kg/week). Tralokinumab crossed the placenta in monkeys.

In a pre- and post-natal development study, doses of up to 100 mg/kg tralokinumab were administered IV to pregnant cynomolgus monkeys once every week from gestation day 20 to parturition. No maternal or developmental toxicity was observed at doses up to 100 mg/kg/week tralokinumab (10 times the MRHD on a mg/kg basis of 10 mg/kg/week).

In an enhanced pre- and post-natal development study, doses of up to 100 mg/kg/week tralokinumab (10 times the MRHD on a mg/kg basis of 10 mg/kg/week) were administered IV to pregnant cynomolgus monkeys once every week from the beginning of organogenesis to parturition. No treatment-related adverse effects on embryofetal toxicity or malformations, or on morphological, functional, or immunological development were observed in the infants from birth to 6 months of age.

The results of the embryofetal developmental study in monkeys will not be included in labeling because this was a pilot study with a small number of animals in each treatment group and can be considered a dose-range–finding study. The results from both the pre- and post-natal development and enhanced pre- and post-natal development studies in monkeys will be included in the labeling, because both of these studies contained adequate numbers of animals in each treatment group for evaluation.

The multiples of human exposure based on mg/kg comparison between the NOAELs identified in pivotal toxicology studies and the proposed MRHD are provided in Table 45.

**Table 45. Multiples of Human Exposure for NOAELs Identified in Pivotal Toxicology Studies**

| Study | Route | NOAEL (mg/kg) | Multiples of Human Exposure[1] (Based on mg/kg Comparison) |
|---|---|---|---|
| Embryofetal development study | IV | 100 | 10 |
| Pre- and post-natal development study | IV | 100 | 10 |
| Enhanced pre- and post-natal development study | IV | 100 | 10 |

Source: Nonclinical study reports submitted to BLA 761180.
[1] Compared with the maximum recommended human dose of 600 mg, or 10 mg/kg on a mg/kg basis.
Abbreviations: IV, intravenous; NOAEL, no observable adverse effect level

Because of the limited information regarding pregnancy impact, pregnancy registries will be recommended as postmarketing requirements, consistent with the Division of Pediatric and Maternal Health consultative review.

# 9. Product Quality

The OPQ, CDER, recommended approval of STN 761180 for (b) (4) manufactured by LEO Pharma A/S follwoing final determination of the compliance status of the (b) (4) (tralokinumab-ldrm) drug substance manufacturing facility. FDA assessment of the ability of these facilities to conduct manufacturing operations in compliance with current good manufacturing practice was required to support approval of the application.

From the product quality and sterility assurance perspective, OPQ, CDER, does not note any product quality deficiencies that would preclude approval of STN 761180 for (b) (4) manufactured by LEO Pharma A/S at this time.

The prelicense inspection was conducted on 03/02/21 to 03/19/2021 at AstraZeneca Pharmaceuticals LP Frederick Manufacturing Center (FEI 3002617771). A three-item FDA

Form 483 was issued and the initial recommendation was withhold. The final classification of the prelicense inspection is acceptable following the Applicant's adequate response to objectionable conditions.

The application will not be approved during this assessment cycle due to Center for Devices and Radiological Health (CDRH) defeciencies. If manufacturing changes are made before the sponsor submits their responses to the CR deficiencies, additional assessment may be needed during the next assessment cycle.

## 9.1. Device or Combination Product Considerations

Not applicable.

# 10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure

Refer to Section III.20 for the results of clinical trial site inspections conducted by the Office of Scientific Investigations, which recommended inspection of one international and three domestic clinical trial sites:

1. ~~Site 273 (Jean-Philippe Lacour in Nice, France): Inspection of this site could not be completed due to Covid restrictions on international travel.~~
2. ~~Site 125(Dr. Nguyen) for ECZTRA 1 Trial.~~
3. ~~Site 810(Dr. Alexis) for Trial ECZTRA 3.~~
4. ~~Site 423(Dr. Parish) for Trial ECZTRA 2.~~

~~The OSI team inspected the 3 domestic sites and recommended the following:~~

- Based on the results of Drs. Alexis and Nguyen's inspections, the studies LP0162-1325 (ECZTRA-1) and LP0162-1339 (ECZTRA-3) appear to have been conducted adequately, and the data generated by these sites appears acceptable in support of the respective indication.
- Dr. Parish's Site 423 was terminated by the Applicant during the trial for noncompliance. "Due to concerns related to study conduct, potential unblinding, and data integrity and reliability noted during the inspection of Dr. Parish's site (in particular with regard to the Week 16 EASI scores), we recommend a sensitivity analysis be conducted with regard to the data from this site."

The Clinical Review team decided to exclude the following three clinical trial sites, which were terminated by the Applicant due to GCP noncompliance, from the efficacy and safety analyses:

(1) Site 423 (Dr. Parish) was terminated during participation in ECZTRA-2.
(2) Site 435 (Dr. Woodson) was terminated during participation in ECZTEND (no compliance issue identified during ECZTRA-2).
(3) Site 818 (Dr. Hanabergh) was terminated during participation in ECZTRA-4 (no compliance issue identified during ECZTRA-3).

The analyses of the safety and efficacy data were not affected in a meaningful way by exclusion of these three sites and support the conclusion that the studies were conducted adequately. The data generated support the proposed indication.

Review of the financial disclosures did not raise any concern about the validity or reliability of the data (refer to Section III.23 for details).

# 11. Advisory Committee Summary

An Advisory Committee meeting was not held, because no unexpected significant safety/efficacy issue or controversial/challenging issue was identified that would benefit from discussion at an Advisory Committee meeting.

# III. Appendices

## 12. Summary of Regulatory History

Investigational new drug (IND) 123797 was submitted on 11/5/2014 for the proposed indication of treatment of atopic dermatitis (AD). The IND-opening study was a Phase 2b study entitled: "A Phase 2b, Randomized, Double-blinded, Placebo-controlled, Dose-ranging Study to Evaluate the Efficacy and Safety of Tralokinumab in Adult Subjects with Moderate-to- Severe Atopic Dermatitis."

Tralokinumab is a human recombinant monoclonal immunoglobulin G4 (IgG4) antibody, an IL-13 receptor α1 and α2 antagonist administered by subcutaneous (SC) injection.

On 9/7/2016, an End-of-Phase 2 meeting was held with the Applicant to discuss their Phase 3 development program, including trial design and analysis, target population, dose and dosing regimen, use of concomitant medications, proposed efficacy endpoints including Patient-Reported Outcomes (PROs) as a primary endpoint (Week 12, later changed to Week 16), use of biomarkers for enrichment, and the safety database.

On 1/30/2017, comments for a Type-C Written Response Only (WRO) Guidance meeting was conveyed to the Applicant, including the Applicant's plans for a drug-drug interaction (DDI) study, proposed Investigator's Global Assessment (IGA) scale, concomitant use of topical corticosteroids (TCS) in the maintenance period, use-related risk analysis, and a human factors validation study to self-administer the product.

On 11/7/2016, the Applicant submitted an initial Pediatric Study Plan (iPSP). On 2/3/2017, the Agency sent an iPSP Written Response letter to the Applicant following discussion of the iPSP at a PeRC meeting on 1/25/2017. On 5/3/2017, the Applicant submitted an Agreed-iPSP which was reviewed by the Division of Dermatology and Dentistry and Division of Pediatric and Maternal Health on 5/25/2017 and discussed at a PeRC meeting on 5/31/2017. On 6/6/2017, the Agency sent a letter of No Agreement to the Agreed-iPSP to the Applicant. On 5/2/2018, the Applicant submitted an Amended PSP, and resubmitted it as an Agreed-iPSP on 6/4/2018. The Agency agreed with the proposed Pediatric Study Plan and the proposed timeline. An Agreed-iPSP agreement letter was sent to the Applicant on 6/28/2018. On 2/28/2020, the Agency sent an agreement letter with an Amended Agreed-iPSP submitted by the Applicant on 11/20/2019. An Inadequate Study Request letter was sent to the Applicant on 6/24/2020 in response to a Proposed Pediatric Study Request submitted by the Applicant on 4/2/2020.

On 2/14/2017, comments for a Type-C WRO Guidance meeting were conveyed to the Applicant, including assessment of pruritus by pruritus numeric rating scale (NRS) score, responder definition ≥4 points in weekly average of Worst Daily Pruritus, and discussion of concerns about Scoring Atopic Dermatitis (SCORAD) and Dermatology Life Quality Index (DLQI) instruments.

On 6/23/2017, an Advice letter was sent to the Applicant including comments related to Clinical Pharmacology, Statistical analysis, and efficacy endpoints for Phase 3 trials.

On 8/22/2017, an Advice letter was sent to the Applicant with comments regarding their proposed outline of a DDI study.

On 11/19/2018, comments for a Type-C WRO Guidance meeting was conveyed to the Applicant, including the Applicant's plan to use pharmacokinetic (PK) data from legacy trials for the development of the population PK (popPK) model of tralokinumab in subjects with AD.

On 5/1/2019, a pre-biologics license application (BLA) meeting was held with the Applicant, and the following were discussed:

- Regulatory: The format for the Table of Contents of the BLA, financial disclosure requirements, and provision of summary-level clinical site data.
- Chemistry, manufacturing, and controls: Inspection of the drug substance and drug product manufacturing sites and plan to cross-reference the Drug Master Files, proposed stability update, the device constituent parts of the combination product, human factors validation study protocol, and product quality microbiology comments.
- Nonclinical: outline of content for the nonclinical part of the application and request for the Applicant to provide an updated carcinogenicity risk assessment.
- Clinical/Biostatistics/Clinical Pharmacology:
  - Agreed that the pivotal Phase 3 trials ECZTRA-1, -2, and -3 and the supportive clinical trials ECZTRA-5 and D2213C00001, combined with PK and safety data from tralokinumab used in other indications, is adequate for filing.
  - Submission of the DDI study as a postmarketing commitment.
  - Submission of complete safety follow-up data (including safety data for subjects in follow-up periods) at the 120-day safety update, electronic common technical document locations for the integrated summary of safety and integrated summary of effectiveness, CDISC formatting of datasets.
  - Agreed with Applicant's plan to report the electrocardiogram (ECG) results in the individual CTRs in Module 5 and in the safety evaluation in Module 2.7.4, and proposed approach for evaluation of QTc prolongation.
  - Agreed to include Summary of PK results from four of six completed Phase 1 trials in the Summary of Clinical Pharmacology Studies and the approach to the population PK analysis plan.
  - The Applicant acknowledged the Agency's comments that formal testing during the maintenance period and testing for DLQI and SCORAD endpoints are not required as findings from this testing will not appear in labeling.
  - Agreed with Applicant's plan to submit the modified statistical analysis plan to the Agency before unblinding the data.
  - Agreed that proposed pooling strategy is acceptable, but analyses based on pooled efficacy data are considered exploratory.
  - Agreed to conduct subgroup analysis for the primary endpoints using the monotherapy pool.
  - Agreed that the total accrued exposure appeared adequate for filing.
  - Agreed with the proposed pooling strategy for AD and monotherapy.
  - Agreed with the Applicant's proposal to include integrated safety information from asthma trials.

- Agreed that the exposure pool include data from all Phase 1 to 3 trials with tralokinumab (AD, healthy subjects, asthma, ulcerative colitis and idiopathic pulmonary fibrosis) to provide a summary of deaths, pregnancies, and rare events, and a summary of major adverse cardiovascular events using the exposure pool and the AD pool.
- Agreed that the safety analysis for subgroups include only the monotherapy pool.
- Agreed with the Applicant's plan to include adverse events of special interest (AESI) based on the mechanism of action of drug, animal toxicity data, and possible class effects (serious infections, opportunistic infections, malignancies, tuberculosis, major adverse cardiovascular events).
- Agreed with the Applicant's planned integrated analysis for investigating immunogenicity in the AD pool.

On 12/10/2019, comments for a Type-C WRO Guidance meeting were conveyed to the Applicant, including chemistry, manufacturing, and controls and stability data, planned PK comparability trials between the two 2.0 mL presentations (accessorized prefilled syringe [APFS] and AI) and the 1.0 mL reference presentation, and the human factors studies.

On 4/27/2020, the Applicant submitted BLA 761180 for tralokinumab-ldrm ( (b) (4) under regulatory pathway 351(a) of the Public Health Service Act, for the indication of "the treatment of moderate-to-severe atopic dermatitis in adult patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable."

# 13. Pharmacology Toxicology: Additional Information and Assessment

## 13.1. Summary Review of Studies Submitted Under the Investigational New Drug

The nonclinical safety profile of tralokinumab supporting this BLA has been adequately evaluated in (1) in vitro and in vivo pharmacology studies, (2) repeat-dose toxicity studies in cynomolgus monkeys (up to 6 months), including safety pharmacology assessment, (3) reproductive and developmental toxicity studies in cynomolgus monkeys, including two fertility, one pilot embryofetal development, one prenatal and postnatal development study, and an enhanced prenatal and postnatal development (ePPND) study, (4) tissue cross-reactivity study in human tissues, and (5) a carcinogenicity risk assessment for tralokinumab. Genotoxicity and carcinogenicity studies were not conducted since they are not considered applicable and/or warranted. PK/Toxicokinetics were studied as part of the toxicity studies and in a separate animal PK study in cynomolgus monkeys.

The target organs of toxicity or off-target tissue binding of the mAb were not identified. Systemic pharmacologic effects did not suggest a potential risk to humans. There were no nonclinical safety issues of significant concern as assessed by the nonclinical studies conducted during the development program.

## 13.1.1. Pharmacology (Primary and Secondary)

Tralokinumab is a human IgG4 monoclonal antibody (mAb) that specifically binds to human IL-13 and inhibits its interaction with IL-13 receptor α1 and α2 subunits (IL-13Rα1 and IL-13Rα2). IL-13 is a naturally occurring cytokine of the type-2 immune response. Tralokinumab inhibits the bioactivity of IL-13 by blocking IL-13 interaction with IL-13Rα1/IL-4Rα receptor complex. Tralokinumab inhibits IL-13–induced responses including the release of proinflammatory cytokines, chemokines and IgE.

A number of in vitro and in vivo pharmacology studies were conducted. The code name for tralokinumab is CAT-354. A briefing summary of the studies previously reviewed is below. Additional pharmacology studies submitted to this BLA are provided in Section 13.2. A brief summary of these pharmacology studies is below.

Tralokinumab had strong affinity for human IL-13 with an equilibrium dissociation constant ($K_D$) of 58pM and dose-dependently inhibited the interaction of IL-13 with both IL-13Rα1 and IL-13Rα2 (Study #RIA354-049 Popovic2017. Refer to Section 13.2).

In vitro studies showed that tralokinumab inhibited the following effects of human IL-13 in a range of primary cell-based assays:

- Neutralized the effects of bacterium-derived human IL-13 (half-maximal inhibitory concentration [$IC_{50}$] 0.37nM), baculovirus-derived human IL-13 ($IC_{50}$ 1.1nM), human IL-13 (Q130R) variant ($IC_{50}$ 1.6nM), and cynomolgus monkey IL-13 ($IC_{50}$ 1.7nM), but not mouse IL-13 in the TF-1 cell proliferation assay (Study #CAT354Rp006).
- Dose-dependently inhibited endogenous human IL-13-induced proliferation in the HDLM-2 cell line ($IC_{50}$ 4.4nM), the release of eotaxin-1 from normal human lung fibroblasts in response to human IL-13 ($IC_{50}$ 0.27nM), and IL-13–induced upregulation of vascular cell adhesion molecule-1 (VCAM-1) on human umbilical vein endothelial cells ($IC_{50}$ 0.37nM) (Study #CAT354Rp006).
- Dose-dependently inhibited IL-13–induced CD23 expression on human peripheral blood mononuclear cells with an $IC_{50}$ of 0.1nM (Study #CAT354Rp039).
- Dose-dependently neutralized IgE production by purified human peripheral cells induced by IL-13 with an $IC_{50}$ of 1.8nM (Study #CAT354Rp029).
- Significantly inhibited potentiation of $Ca^{2+}$-signaling histamine bronchial smooth muscle contraction at the single antibody concentration tested (67nM) using primary human bronchial smooth muscle cells (Study #CAT354Rp025).
- Dose-dependently decreased release of eotaxin ($IC_{50}$ 32.4nM) and inhibited eosinophil shape change with an $IC_{50}$ of 14nM in granulocytes purified from human buffy coats (Study #CAT354Rp042).
- Dose-dependently inhibited gene expression of CCL2 ($IC_{50}$ 201pM), CCL26 ($IC_{50}$ 189pM), NTRK1 ($IC_{50}$ 268pM) and IL13RA2 ($IC_{50}$ 367pM), as well as secretion of CCL-2/MCP-1 ($IC_{50}$ 217pM) induced by IL-13 in human epidermal keratinocytes (Study #REP-HND-2019-02 [Section 13.2]).
- Dose-dependently inhibited downregulation of FLG ($IC_{50}$ 19.1 nM), FLG2 ($IC_{50}$ 16.4nM), LOR ($IC_{50}$ 16.0nM and 13.3nM), ELOVL3 ($IC_{50}$ 16.2 nM), and DEFB4A ($IC_{50}$ 13.0nM) mediated by IL-13 in human epidermal keratinocytes (Study #REP-HND-2019-03 [Section 13.2]).

- Dose-dependently inhibited gene expression of CCL2 ($IC_{50}$ 315pM), CCL11 ($IC_{50}$ 112pM), and POSTN ($IC_{50}$ 241pM), as well as secretion of CCL-2/MCP-1 ($IC_{50}$ 336pM) induced by IL-13 in human dermal fibroblasts (Study #REP-HND-2019-04 [Section 13.2]).

In in vivo studies tralokinumab inhibited or decreased the following responses involving IL-13:

- Dose-dependently inhibited IL-13–induced infiltration of total leukocytes and eosinophils in a mouse air pouch model (Study #CAT354Rp037).
- Pretreatment with tralokinumab significantly reduced airway hyperresponsiveness (AHR) and bronchoalveolar lavage eosinophilia in BALB/C male mice (Study #CAT354Rp043).
- Tralokinumab caused a 60% inhibition of total serum IgE levels by seven days after administration in female allergic cynomolgus monkeys with high baseline IgE levels (Study #CAT354Rp034).
- Inhibited AHR measured by PC30 inhibited AHR, measured by area under the antigen challenge lung resistance-time curve ($R_L$ AUC) ($p<0.05$). Inhibited antigen priming ($p<0.01$). Inhibited eosinophil ($p<0.05$) and total cell ($p<0.05$) but not macrophage, lymphocyte, or mast cell influx into the bronchoalveolar lavage in a cynomolgus monkey antigen challenge model (Study #CAT354Rp038).

Tralokinumab did not neutralize bioactivity of IL-4 or IL-1β in the VCAM-1 human umbilical vein endothelial cell assay (Study #CAT354Rp006) and the IgE production induced by IL-4 (Study #CAT354Rp029). Tralokinumab did not inhibit downregulation of FLG, FLG2, LOR, ELOVL3, and DEFB4A; gene expression of CCL2, CCL11 and POSTN; or secretion of CCL-2/MCP-1 mediated/ induced by IL-4 (Studies #REP-HND-2019-02 and #REP-HND-2019-03).

No cross-reactivity of tralokinumab-fluorescein isothiocyanate (FITC) with tested normal human tissues was observed (Study #530762. Refer to Other Toxicology/Specialized Studies under Section 13.1.4 for details).

The IL-13 amino acid sequence homology between human and cynomolgus monkey is 95%, whereas that between human and rodent is 55% for mouse and 62% for rat. Tralokinumab did not cross-react with mouse IL-13. Tralokinumab neutralized the effect of cynomolgus monkey IL-13 with near-equivalent potency to wildtype human IL-13. Therefore, cynomolgus monkey was selected as a single pharmacologically relevant species for use in nonclinical studies with tralokinumab.

### 13.1.2. Safety Pharmacology

No stand-alone safety pharmacology study was conducted with tralokinumab. Safety pharmacology parameters were included in the repeat-dose toxicology studies in cynomolgus monkeys. Repeated administration of tralokinumab up to 100 mg/kg/week had no adverse effects on the evaluated parameters for cardiovascular, respiratory, and behavioral effects. Neurobehavioral assessment was included for infants in an ePPND study. No tralokinumab-related effects were observed in offspring from pregnant female cynomolgus monkeys treated with tralokinumab up to 100 mg/kg/week during the period of organogenesis through parturition.

## 13.1.3. Absorption, Distribution, Metabolism, Excretion / Pharmacokinetics

Absorption studies were conducted with tralokinumab in a separate PK study and toxicokinetic studies incorporated in toxicology studies in cynomolgus monkeys (Table 46). Standard distribution, metabolism, and excretion studies were not conducted with tralokinumab because it is a monoclonal antibody. The code name for tralokinumab is CAT-354.

**Table 46. Absorption, Distribution, Metabolism, Excretion, PK and TK Studies**

| Type of Study | Major Findings |
|---|---|
| **Absorption**<br>Investigation of the intravenous single-dose pharmacokinetics of CAT-354 in Ascaris suum-sensitive cynomolgus monkey, Study #CAT354Rp034, nonGLP | Single Dose of 10 mg/g to Monkeys<br>$T_{1/2}$: 10.8 days<br>$AUC_{0-\infty}$: 1954 µg day/mL<br>$C_{max}$: 353.3 µg/mL<br>$C_L$ or $C_{L/F}$: 5.5 mL/kg/day<br>$V_z$: 85.0 mL/kg |
| **Distribution**<br>No organ/tissue and other distribution studies were conducted. | The $V_z$ of tralokinumab was 85.0 mL/kg after a single intravenous dose, indicating minimal to moderate extravascular distribution. Tralokinumab shows the PK behavior expected for an IgG4 antibody targeted to a soluble cytokine. For this reason, as well as due to the lack of target organ toxicity, specific tissue distribution studies were not considered relevant. |
| **Metabolism**<br>No metabolism studies were conducted. | The expected consequence of the metabolism of monoclonal antibodies is degradation to small peptides and individual amino acids. |
| **TK Data from general toxicology studies**<br>CAT-354: 28-Day (Once Weekly Dosing) Intravenous Administration Toxicity Study in Monkey Followed by a 28-Day Recovery Period, Study #1348/053 and CAT-354Rp012, GLP | 4-Week IV Administration to Monkeys<br>*$T_{1/2}$*<br>100 mg/kg: 6.7 days<br>*$AUC_{0-t}$*<br>10 mg/kg: 1270 µg day/mL<br>30 mg/kg: 4580 µg day/mL<br>100 mg/kg: 18,800 µg day/mL<br>*$C_{max}$*<br>10 mg/kg: 297 µg/mL<br>30 mg/kg: 1020 µg/mL<br>100 mg/kg: 4410 µg/mL<br>*Accumulation*<br>N/A<br>*Dose proportionality*<br>Increased approximately dose-proportionally from 10 to 100 mg/kg following the first and fourth doses.<br>*ADA*<br>None |

| Type of Study | Major Findings |
|---|---|
| CAT-354: 13-Week (Once Weekly Dosing) Intravenous Administration Toxicity Study in Monkey with a 13-Week Treatment-Free Period, Study #1348/058, GLP | 13-Week IV Administration to Monkeys<br>**Male**<br>*$T_{1/2}$*<br>10 mg/kg: 15.7 days<br>100 mg/kg: 10 days<br>*$AUC_{0.5-144}$*<br>10 mg/kg: 1480 µg day/mL<br>30 mg/kg: 4060 µg day/mL<br>100 mg/kg: 22,600 µg day/mL<br>*$C_{max}$*<br>10 mg/kg: 550 µg/mL<br>30 mg/kg: 1830 µg/mL<br>100 mg/kg: 6760 µg/mL<br>**Female**<br>*$T_{1/2}$*<br>10 mg/kg: 17.4 days<br>100 mg/kg: 9.5 days<br>*$AUC_{0.5-144}$*<br>10 mg/kg: 2000 µg day/mL<br>30 mg/kg: 7250 µg day/mL<br>100 mg/kg: 22,000 µg day/mL<br>*$C_{max}$*<br>10 mg/kg: 509 µg/mL<br>30 mg/kg: 2120 µg/mL<br>100 mg/kg: 5340 µg/mL<br>*Accumulation*<br>N/A<br>*Dose proportionality*<br>Increased approximately dose-proportionally from 10 to 100 mg/kg.<br>*ADA*<br>Four of twenty-six tralokinumab-treated monkeys developed ADAs during the recovery phase. |

| Type of Study | Major Findings |
|---|---|
| CAT-354: 26-Week Intravenous Toxicity Study in Cynomolgus Monkeys with a 13-Week Treatment-Free Period, Study #CRL509615, GLP | <u>26-Week IV Administration to Monkeys</u><br>**Male**<br>$T_{1/2}$<br>10 mg/kg: 15.8 days<br>30 mg/kg: 17.0 days<br>100 mg/kg: 12.9 days<br>$AUC_{0-168}$<br>10 mg/kg: 2280 µg day/mL<br>30 mg/kg: 8700 µg day/mL<br>100 mg/kg: 28,900 µg day/mL<br>$C_{max}$<br>10 mg/kg: 506 µg/mL<br>30 mg/kg: 1780 µg/mL<br>100 mg/kg: 5992 µg/mL<br>**Female**<br>$T_{1/2}$<br>10 mg/kg: 9.1 days<br>30 mg/kg: 11.6 days<br>100 mg/kg: 10.8 days<br>$AUC_{0-168}$<br>10 mg/kg: 2700 µg day/mL<br>30 mg/kg: 8320 µg day/mL<br>100 mg/kg: 28,100 µg day/mL<br>$C_{max}$<br>10 mg/kg: 563 µg/mL<br>30 mg/kg: 1868 µg/mL<br>100 mg/kg: 5947 µg/mL<br>*Accumulation*<br>Systemic exposure increased three- to six-fold over the 26-week treatment period.<br>*Dose proportionality*<br>Increased in an approximately dose-proportional manner over the dose range of 10 to 100 mg/kg.<br>*Gender differences*<br>No significant gender differences.<br>*ADA*<br>None |

| Type of Study | Major Findings |
|---|---|
| CAT-354: 13-Week Toxicity Study in the Cynomolgus Monkey with an 8-Week Recovery Period Following Subcutaneous Administration, Study #CRL514981, GLP | 13-Week SC Administration to Monkeys<br>$T_{1/2}$<br>75 mg: 10.9 days<br>150 mg: 11.3 days<br>300 mg: 11.8 days<br>$AUC_{0-144}$<br>75 mg: 9130 µg day/mL<br>50 mg: 19,300 µg day/mL<br>300 mg: 38,800 µg day/mL<br>$C_{max}$<br>10 mg: 2160 µg/mL<br>50 mg: 4610 µg/mL<br>300 mg: 8850 µg/mL<br>*Accumulation (AR)*<br>75 mg: 5.2<br>150 mg: 5.2<br>300 mg: 5.8<br>*Gender differences*<br>No significant difference<br>*ADA*<br>Twenty three of the 144 samples tested were reported positive. This represents six control animals (12 samples) and nine animals (11 samples) from tralokinumab-treated groups. |
| **TK Data from reproductive toxicology studies**<br>CAT-354: 13-Week Subcutaneous Administration Male Fertility Study in the Cynomolgus Monkey with a 13-Week Recovery Phase, Study #2843-005, GLP | Male Monkeys (14th Dose on Day 92)<br>$T_{1/2}$<br>200 mg: 17.4 days<br>600 mg: 15.6 days<br>$T_{max}$<br>200 mg: 3 days<br>600 mg: 3 days<br>$AUC_{0-7}$<br>200 mg: 10,800 µg day/mL<br>600 mg: 19,000 µg day/mL<br>$C_{max}$<br>200 mg: 1730 µg/mL<br>600 mg: 3010 µg/mL<br>*CL/F*<br>200 mg: 21.1 mL/day<br>600 mg: 36.6 mL/day<br>*Accumulation (AR)*<br>200 mg: 5.3<br>600 mg: 4.3<br>*ADA*<br>None |

| Type of Study | Major Findings |
|---|---|
| CAT-354: A Subcutaneous Administration Female Fertility Study in the Cynomolgus Monkey with a Recovery Phase, Study #2843-006, GLP | Female Monkeys (12th Dose on Day 79)<br>*$T_{1/2}$*<br>100 mg: 12.4 days<br>350 mg: 12.1 days<br>*$T_{max}$*<br>100 mg: 3 days<br>350 mg: 3 days<br>*$AUC_{0-7}$*<br>100 mg: 4920 µg day/mL<br>350 mg: 21,100 µg day/mL<br>*$C_{max}$*<br>100 mg: 782 µg/mL<br>350 mg: 3360 µg/mL<br>*CL/F*<br>100 mg: 20.4 mL/day<br>350 mg: 17.6 mL/day<br>*Accumulation (AR)*<br>100 mg: 4.8<br>350 mg: 4.1<br>*ADA*<br>None |
| A Pilot Embryofetal Development Toxicity Study of CAT-354 Administered by Intravenous Injection to Pregnant Cynomolgus Monkeys, Study #SNBL200.07, GLP | Female Monkeys<br>*$T_{1/2}$*<br>10 mg/kg: 4 days<br>30 mg/kg: 5.4 days<br>100 mg/kg: 5.7 days<br>*$AUC_{48-55}$*<br>10 mg/kg: 1090 µg day/mL<br>30 mg/kg: 3590 µg day/mL<br>100 mg/kg: 11,100 µg day/mL<br>*$C_{max}$*<br>10 mg/kg: 341 µg/mL<br>30 mg/kg: 1140 µg/mL<br>100 mg/kg: 3690 µg/mL<br>*CL*<br>10 mg/kg: 11 mL/day/kg<br>30 mg/kg: 14.7 mL/day/kg<br>100 mg/kg: 6.3 mL/day/kg<br>*Dose proportionality*<br>Increased in a dose-proportional manner over the period GD 48 to 55 ($AUC_{48-55}$).<br>*Ratio of tralokinumab concentrations in fetal and maternal serum*<br>10 mg/kg: 53.8±29.7%<br>30 mg/kg: 53.1±29.3%<br>100 mg/kg: 363±446%*<br>* The reason the ratio for the 100 mg/kg group was so high is an unusually low maternal animal concentration (0.426±0.153 µg/mL in the HD vs. 5.190±4.196 µg/mL in the MD group) and an usually high level in one fetus from the HD group (6.46 µg/mL) compared to the mean of the other three in the HD group (0.50 µg/mL).<br>*ADA*<br>None |

| Type of Study | Major Findings |
|---|---|
| An Assessment of the Effects of CAT-354 on Pre- and Post-Natal Development When Administered Weekly by Intravenous Injection to Pregnant Cynomolgus Monkeys, Study #SNBL.200.15, GLP | Female Monkey<br>$T_{1/2}$<br>30 mg/kg: 6.8 days<br>100 mg/kg: 9.3 days<br>$C_{min}$<br>30 mg/kg: 452 µg/mL<br>100 mg/kg: 2062 µg/mL<br>$C_{max}$<br>30 mg/kg: 910 µg/mL<br>100 mg/kg: 4001 µg/mL<br>*Tralokinumab levels in lactating monkeys*<br>LD 7<br>30 mg/kg: 240 µg/mL<br>100 mg/kg: 1187 µg/mL<br>LD 14<br>30 mg/kg: 119 µg/mL<br>100 mg/kg: 741 µg/mL<br>LD 28<br>30 mg/kg: 30 µg/mL<br>100 mg/kg: 330 µg/mL<br>*Tralokinumab levels in F1 neonate monkeys*<br>PND 7<br>30 mg/kg: 336 µg/mL<br>100 mg/kg: 1263 µg/mL<br>PND 14<br>30 mg/kg: 209 µg/mL<br>100 mg/kg: 901 µg/mL<br>PND 28<br>30 mg/kg: 121 µg/mL<br>100 mg/kg: 488 µg/mL<br>*ADA*<br>One 100 mg/kg/week maternal animal tested positive during the treatment period. |

| Type of Study | Major Findings |
|---|---|
| Enhanced Pre-Postnatal Toxicity of CAT-354 Administered by Intravenous Infusion in Pregnant Cynomolgus Monkeys with 6-Month Postnatal Evaluation, Study# 20054081, GLP | Female Monkeys<br>*$AUC_{0-7}$*<br>30 mg/kg: 6550 µg day/mL<br>100 mg/kg: 20,300 µg day/mL<br>*$C_{max}$*<br>30 mg/kg: 1280 µg/mL<br>100 mg/kg: 3940 µg/mL<br>*Dose proportionality*<br>Exposure to tralokinumab in maternal monkeys increased from 30 to 100 mg/kg/week in a generally dose-proportional manner. In the infant monkeys, exposure increased with the increase in tralokinumab dose level from 30 to 100 mg/kg/week administered to the maternal monkeys.<br>*Accumulation*<br>Observed after multiple doses. Maternal to infant ratios of tralokinumab concentrations in serum on PPD91/BD91:<br>30 mg/kg: 0.539<br>100 mg/kg: 0.143<br>Tralokinumab was generally detectable in maternal and infant animals up to PPD/BD91, but generally below or slightly above the detection limit (maternal only) on PPD/BD180±2.<br>*ADA*<br>ADA-positive samples occurred in maternal animals (control: 11/170, 30 mg/kg: 4/160 and 100 mg/kg: 5/166 samples) and infants (14/31, 12/30, and 15/30 samples from control, 30 mg/kg/week and 100 mg/kg/week infant monkeys, respectively) at a low incidence that was comparable across all groups, including controls. The reason for ADA positivity in control samples was not determined, but the overall results suggested a relation to assay performance. |

Source: Nonclinical study reports submitted to BLA 761180.
Abbreviations: ADA, antidrug antibodies, AR, accumulation ratio; $AUC_{0-7}$, area under the concentration–time curve from 0 to 7 h; $AUC_{0-144}$, area under the concentration–time curve from 0 to 144 h; $AUC_{0-168}$, area under the concentration–time curve from 0 to 168 h; $AUC_{0.5-144}$, area under the concentration–time curve from 0.5 to 144 h; $AUC_{0-t}$, area under the concentration–time curve from time 0 to time t; $AUC_{0-\infty}$, area under the concentration–time curve from time 0 to infinity; $AUC_{48-55}$, area under the concentration–time curve from 48 to 55 h; BD, birth day; CL, clearance; CL/F, clearance after oral administration; $C_{max}$, maximum concentration; $C_{min}$, minimum concentration; GLP, good laboratory practices; HD, high dose; IgG, immunoglobulin G; IV, intravenous; LD, lactational day or low dose; MD, mid dose; N/A, not applicable; PND, postnatal day; PK, pharmacokinetics; PPD, postpartum day; SC, subcutaneous; $T_{1/2}$, terminal half-life; TK, toxicokinetics; $T_{max}$, time to $C_{max}$; $V_z$, terminal-phase volume of distribution

# 13.1.4. Toxicology

## 13.1.4.1. General Toxicology

### Single-Dose Toxicity

No single-dose toxicity studies were performed with tralokinumab. No acute toxicity after the first dose of tralokinumab was noted at doses up to 100 mg/kg intravenous (IV) or 300 mg/injection SC in the repeat-dose toxicity studies in cynomolgus monkeys.

### Repeat-Dose Toxicity

Three IV and two SC repeat-dose toxicity studies were submitted. The no observed adverse effect level (NOAEL) for tralokinumab in cynomolgus monkeys was 90 mg/kg/week in the 13-week SC toxicology study and 100 mg/kg/week in the 26-week IV toxicology study. No tralokinumab-related adverse effects (including effects on the immune system) were observed.

No target organs of toxicity were identified. There were no neoplastic or test article-related non-neoplastic proliferative lesions in the 26-week IV toxicology study. The NOAEL of 100 mg/kg/week in the 26-week IV toxicology study is 10 times the MRHD based on a mg/kg of 10 mg/kg/week. The mean $AUC_{0\text{-}168h}$ values associated with the NOAEL are 694,805 and 677,731 µg hr/mL for males and females, respectively, which are 18 times the MRHD based on AUC comparison for males and females. The multiples based on AUC comparison were compared with the human AUC value at steady state at the MRHD, 1583.3 µg day/mL (refer to Section 14. The code name for tralokinumab is CAT-354.

**Study 1 CAT-354: 26-Week Intravenous Toxicity Study in Cynomolgus Monkeys With a 13-Week Treatment-Free Period (Study #CRL509615)**

*Key Study Findings*

- No tralokinumab-related adverse effect was observed.
- No target organ of toxicity was identified.
- The NOAEL was 100 mg/kg.
- The mean $AUC_{0\text{-}168h}$ values associated with the NOAEL were 694,805 µg day/mL in males and 677,731 µg day/mL in females, and the mean maximum concentration ($C_{max}$) values were 3362 µg/mL in males and 3253 µg/mL in females at Week 26.

*Study Information*

| Study Features and Methods | Details |
|---|---|
| GLP compliance: | Yes |
| Dose and frequency of dosing: | 0, 10, 30 and 100 mg/kg weekly. |
| Route of administration: | Intravenous |
| Formulation/vehicle: | Solution/ (b) (4) sodium acetate, (b) (4) sodium chloride, (b) (4) polysorbate 80, pH 5.5. |
| Species/strain: | Monkeys/Cynomolgus monkeys (*Macaca fascicularis*). |
| Number/sex/group: | 4 |
| Age: | Between 13 and 19 months of age on arrival. |
| Satellite groups/unique design: | 3/sex/group for recovery, except group 2. |
| Deviation from study protocol affecting interpretation of results: | None |

*Observations and Results*

| Parameter | Major Findings |
|---|---|
| Mortality | All animals survived until their scheduled necropsy. |
| Clinical signs | No treatment related findings were observed. |
| Body weights | No treatment related changes were observed. |
| Ophthalmoscopy | No treatment related changes were observed. |
| Electrocardiogram | No treatment related findings were observed. |
| Hematology | No treatment related changes were observed. |
| Clinical chemistry | No treatment related changes were observed. |
| Urinalysis | No treatment related changes were observed. |
| Gross pathology | No treatment related findings were observed. |
| Organ weights | No treatment related changes were observed. |
| Histopathology<br>Adequate battery: Yes | There were no notable treatment related findings. |
| Immunophenotyping and antidrug antibodies | Treatment related effects on biomarkers for T, B, and natural killer cells, and for expression of Fc receptors in the lymphocytes and monocytes were not observed. No substantive evidence for the presence of antidrug antibodies in any serum samples examined. |

**Study 2 CAT-354: 28-Day (Once-Weekly Dosing) Intravenous Administration Toxicity Study in the Monkey Followed by a 28-Day Recovery Period (Study #1348/053, GLP)**

In this 28-day intravenous toxicity study in cynomolgus monkeys (3/sex/group) with a 28-day recovery period (2/sex/group in the vehicle control and high-dose groups), tralokinumab was administered at dose levels of 0 (vehicle control; phosphate-buffered saline), 10, 30, and 100 mg/kg once weekly. The maximum feasible dose is 100 mg/kg, per the Applicant. There were no treatment-related adverse effects on clinical observations, body weight, ophthalmic findings, ECG examinations, clinical pathology, organ weights, or macroscopic and microscopic pathology. The NOAEL was 100 mg/kg based on the results of this study, which resulted in a mean combined $AUC_{0\text{-}144h}$ value of 451,422 µg day/mL and $C_{max}$ value of 4412 µg/mL following final dose administration on Day 22.

**Study 3: CAT-354: 13-Week (Once-Weekly Dosing) Intravenous Administration Toxicity Study in the Monkey with a 13-Week Treatment-Free Period (Study #1348/058, GLP)**

In a 13-week intravenous toxicity study in cynomolgus monkeys (3/sex/group) with a 13-week recovery period (2/sex/group in vehicle control, low and high dose groups), tralokinumab was administered at dose levels of 0 (vehicle control; phosphate buffered saline), 10, 30, and 100 mg/kg once weekly. There were no treatment-related adverse effects on clinical observations, body weight, ophthalmic findings, ECG examinations, clinical pathology, organ weights, or macroscopic and microscopic pathology. The NOAEL was 100 mg/kg based on the results of this study, which resulted in mean $AUC_{0\text{-}144h}$ values of 542,000 µg day/mL in males and 528,000 µg day/mL in females, and $C_{max}$ values of 6760 µg/mL in males and 5340 µg/mL in females at Week 13. There were nine antidrug antibodies (ADA)-positive samples in total; four from vehicle control animals and five from tralokinumab-treated animals. The four samples deemed positive from the vehicle control group were from two individuals. The five samples deemed positive from the tralokinumab-treated groups were from four individuals, three from the

10 mg/kg group and one from the 100 mg/kg group. There was no apparent effect of ADA formation on tralokinumab exposure.

**Study 4: 28-Day Toxicological Bridging Study for CAT-354 in Male Cynomolgus Monkeys Using Subcutaneous Administration (Study #CRL513066, GLP)**

In a 28-day bridging study, tralokinumab was administered SC to male cynomolgus monkeys (three/group) at doses of 75, 150, and 225 mg/injection. Data for control animals were not reported, and the number (three) of animals/group was small. The Applicant subsequently conducted a 13-week bridging subcutaneous toxicity in cynomolgus monkey as per the recommendation of the Agency.

**Study 5: CAT-354: 13-Week Toxicity Study in the Cynomolgus Monkey with an 8-Week Recovery Period Following Subcutaneous Administration (Study #CRL514981, GLP)**

In this 13-week study, tralokinumab was administered by SC injection to cynomolgus monkeys (six/sex/group) at dose levels of 0 (vehicle control; (b) (4) sodium acetate, (b) (4) sodium chloride, (b) (4) polysorbate 80 at pH 5.5), 75, 150, or 300 mg/injection/animal once weekly. T s per sex per group were sacrificed on Day 92 after 13 weeks of dosing with the remaining three/sex/group sacrificed on Day 148 after an additional 8 weeks of observation.

There were no treatment-related adverse effects on clinical observations, body weight, ophthalmic findings, ECG examinations, clinical pathology, organ weights, or macroscopic and microscopic pathology. The NOAEL was 300 mg/week (approximately 90 mg/kg/week) based on the results of this study, which resulted in mean steady-state combined AUC and $C_{max}$ values of 38,800±4440 µg day/mL and 8850±1560 µg/mL, respectively.

Twenty three of the one hundred forty-four samples tested were reported as positive for the presence of anti-CAT-354 antibodies. This represents six control animals (12 samples) and nine animals (11 samples) from tralokinumab-treated groups. The presence of ADA had no impact on the observed exposure to tralokinumab.

It was determined that this 13-week subcutaneous toxicity study conducted with tralokinumab in cynomolgus monkeys provided an adequate bridge to the 13-week and 26-week intravenous toxicity studies conducted with tralokinumab in cynomolgus monkeys due to the similar toxicity profiles noted after repeat-dose SC versus IV administration.

#### 13.1.4.2. Genetic Toxicology

Genetic toxicology studies are not applicable to monoclonal antibodies and were not conducted with tralokinumab based on the International Council on Harmonisation (ICH) S6 guidance.

## Carcinogenicity

Carcinogenicity studies have not been conducted with tralokinumab in any species. The Applicant provided an updated carcinogenicity risk assessment for tralokinumab in this BLA submission. No significant changes have been made to the original carcinogenicity risk assessment for tralokinumab that was reviewed under the IND. The Executive Carcinogenicity Assessment Committee provided their concurrence with the carcinogenicity risk assessment for

tralokinumab submitted under the IND during an Executive Carcinogenicity Assessment Committee meeting on 7/15/2011. The Applicant was advised that "A 2-year carcinogenicity study with tralokinumab is not needed. However, subjects enrolled in clinical trials with tralokinumab should be monitored for potential development of tumors" on 08/12/2011 under the IND. Weight of evidence from the literature does not raise safety concerns regarding malignancy based on an evaluation of the available literature related to IL-13 inhibition. There was no evidence of tissue proliferation (i.e., hyperplasia, preneoplastic lesions) or immunosuppression in the 6-month intravenous toxicology study in cynomolgus monkeys that received tralokinumab at doses of up to 100 mg/kg/week.

#### 13.1.4.3. Reproductive Toxicology

The Applicant submitted final study reports for two subcutaneous fertility studies, an intravenous pilot embryo-fetal developmental study, an intravenous prenatal and postnatal development study and an intravenous ePPND study in cynomolgus monkeys. The code name for tralokinumab is CAT-354.

## Fertility and Early Embryonic Development

**Study 1 CAT-354: 13-Week Subcutaneous Administration Male Fertility Study in the Cynomolgus Monkey With a 13-Week Recovery Phase (Study #2843-005, GLP)**

Tralokinumab was administered SC to sexually mature male cynomolgus monkeys (six/group) at 0 (vehicle control; (b) (4) sodium acetate, (b) (4) sodium chloride, (b) (4) polysorbate 80 at pH 5.5), 200, or 600 mg/animal/week for 14 doses over 13 weeks. Three animals per group were sacrificed on Day 95 (3 days after the last dose) with the remaining three per group sacrificed on Day 184 after an additional 13 weeks of observation.

All animals survived to their scheduled necropsy. No tralokinumab-related adverse effects were noted for clinical signs, body weight, T-cell–dependent antigen response (anti-keyhole limpet hemocyanin antibody), organ weights, or macroscopic and microscopic pathology nor for male reproductive parameters (including epididymal sperm motility, flow cytometrically analyzed testicular tissues, testicular size, semen evaluation, ejaculate weight, sperm count, sperm motility, and morphology). The NOAEL was 600 mg/week (100 mg/kg/week for a 6 kg male monkey) based on the results from this study, which resulted in a mean AUC of 19,000±8650 µg day/mL and a mean $C_{max}$ of 3010±881 µg/mL following the 14$^{th}$ dose.

**Study 2 CAT-354: A Subcutaneous Administration Female Fertility Study in the Cynomolgus Monkey With a Recovery Phase (Study #2843-006, GLP)**

Tralokinumab was administered by SC injection to sexually mature female cynomolgus monkeys (6/group) at dose levels of 0 (vehicle control; (b) (4) sodium acetate, (b) (4) sodium chloride, (b) (4) polysorbate 80 at pH 5.5), 100, and 350 mg/animal once weekly for three consecutive menstrual cycles (maximum of 15 doses). Three animals per group were sacrificed after completion of their third treatment cycle with the remaining three per group sacrificed after completion of their third recovery cycle.

No tralokinumab-related adverse effects were observed for clinical signs, body weight, T-cell–dependent antibody response, organ weights, or macroscopic and microscopic pathology. No

tralokinumab-related effects were observed on female reproductive parameters, including menstrual cycle and organ weights (ovaries, cervix, and vagina), macroscopic and microscopic analysis (ovaries, cervix, vagina, ureter, and urinary bladder). The NOAEL was 350 mg/week (100 mg/kg/week for 3.5 kg female monkey) based on the results of this study, which resulted in a mean AUC of 21,100±5200 µg day/mL and a mean $C_{max}$ of 3360±788 µg/mL following the $12^{th}$ dose.

No development toxicity studies with tralokinumab were conducted to evaluate early embryonic development to implantation as it is not practical to do via mating studies in cynomolgus monkeys.

## Embryonic Fetal Development

**Study 1 A Pilot Embryo-Fetal Development Toxicity Study of CAT-354 Administered by Intravenous Injection to Pregnant Cynomolgus Monkeys (Study #SNBL200.07)**

GLP compliance: Yes

*Key Study Findings*

- No test article-related effects were noted in maternal animals.
- No test article-related effects were noted in fetal examinations.
- The NOAEL for maternal and developmental toxicity was 100 mg/kg/week.
- The $AUC_{GD48-55}$ and $C_{max}$ values are 11,100 µg day/mL and 3,690 µg/mL, respectively.
- Percent of placental transfer is 53.8±29.7%, 53.1±29.3%, and 363±446% in the 10 mg/kg, 30 mg/kg, and 100 mg/kg groups, respectively.
- No monkey antihuman antibody response was detected.

*Methods*

| Parameter | Method Details |
|---|---|
| Dose and frequency of dosing: | 0 (vehicle), 10, 30 and 100 mg/kg weekly from gestation day (GD) 20 to GD 48 (total of five doses). |
| Route of administration: | Intravenous infusion |
| Formulation/vehicle: | Solution (b) (4) acetate, (b) (4) odium chloride and (b) (4) polysorbate 80, pH 5.5 |
| Species/strain: | Monkeys/naïve cynomolgus monkeys |
| Number/sex/group: | 4 pregnant animals/group |
| Satellite groups: | None |
| Study design: | Females were mated with males for three consecutive days. The middle day of the mating period was designated as GD 0. Animals were dosed once weekly on GDs 20, 27, 34, 41, and 48 to coincide with the time of organogenesis from GD 20 to GD 50. On GD 100, the animals were sacrificed and the fetuses were removed by cesarean section to evaluate for developmental toxicity. |
| Deviation from study protocol affecting interpretation of results: | None |

*Observations and Results*

| Parameter | Major findings |
|---|---|
| Mortality | No unscheduled deaths. |
| Clinical signs | No test article-related clinical signs were observed during the study. |
| Body weights and food consumption | No test article-related effects on maternal body weight and food consumption were noted. |
| Necropsy findings<br>Cesarean section data | A total of 14 fetuses was obtained by scheduled cesarean section. All of these fetuses were delivered alive with no external anomalies observed. No abnormalities in fetal weight and placental weight. |
| Necropsy findings Offspring | No test article-related effects on fetal organ weight. No test article-related fetal visceral and skeletal abnormal findings |

## Prenatal and Postnatal Development

**Study 1: An Assessment of the Effects of CAT-354 on Pre- and Post-Natal Development When Administered Weekly by Intravenous Injection to Pregnant Cynomolgus Monkeys (Study #SNBL.200.15)**

GLP compliance: Yes

*Key Study Findings*

- No test article related adverse effects on maternal, fetal, or infant parameters.
- The NOAEL for maternal and developmental toxicity was 100 mg/kg/week.
- The maternal gestation day (GD) 153 $C_{max}$ was 4001 µg/mL and infant postnatal day 7 tralokinumab exposure was 1263 µg/mL.

*Methods*

| Parameter | Method Details |
|---|---|
| Dose and frequency of dosing: | 0 (vehicle), 30 and 100 mg/kg once a week from gestation day (GD) 20 to natural delivery (approximately GD 160). |
| Route of administration: | Intravenous |
| Formulation/vehicle: | Solution/ (b) (4) acetate, (b) (4) sodium chloride and (b) (4) polysorbate 80, pH 5.5. |
| Species/strain: | Monkeys/Cynomolgus monkeys (*Macaca fascicularis*). |
| Number/sex/group: | 16 females/group |
| Satellite groups: | None |
| Study design: | Pregnancy was determined by ultrasound monitoring. For maternal animals, clinical observations, pregnancy monitoring, estimates of food consumption and body weights were collected throughout the study. Blood samples for toxicokinetic (TK) and anti-CAT-354 antibody (Ab) were collected at predose on GD20, predose and approximately 30 min postdose on GDs 104, 132, and 153; and once on lactation days (LDs) 7, 14, and 28.<br>For F1 neonates, birth examination (viability, sex determination, and external formation), clinical observations, body weight, functional and morphological development, and ophthalmology data were collected. Blood samples for TK/Ab were collected from F1 neonates on postnatal days (PNDs) 7, 14, and 28. In addition, breast milk for TK/Ab assays were collected from lactating maternal animals once on LDs 7, 14, and 28. F1 neonates were necropsied between PND 28 and 31. On the day of necropsy, X-ray photographs were taken for skeletal examination. Organ weights were measured, and organs/tissues were collected and preserved in 10% neutral buffered formalin (except for eyes including optic nerves and testes, which were fixed in modified Davidson's fluid). |
| Deviation from study protocol affecting interpretation of results: | None |

*Observations and Results*

F0 Dams

| Parameter | Major Findings |
|---|---|
| Mortality | There were no maternal deaths or unscheduled sacrifices. |
| Clinical signs | No test article-related clinical findings were noted. |
| Pregnancy monitoring | No test article-related abortifacient effect. |

| Parameter | Major Findings |
|---|---|
| Gestation length | A slight decrease in gestation length observed at 100 mg/kg was considered nonadverse.<br>A slightly shorter gestation length was observed in the 100 mg/kg/week group (average 155 days) compared to controls (average 160 days) but individual gestation length was within normal range for most of the neonates.<br>The increased incidence of slightly reduced gestation length for 100 mg/kg/week animals was associated in many cases with slight reductions of birth weight, as might normally be expected. It was considered that the average birth weight reduction was adequately explained by the differences in gestation length, and in view of the fact that all the neonates in the 100 mg/kg group showed adequate growth after birth, the biological significance of the intergroup differences in this study was considered uncertain and nonadverse, even if possibly test article-related. |
| Body weight and food consumption | No test article-related effects on maternal body weight and food consumption were noted. |
| Cesarean section data | Emergency Cesarean section was performed when embryonic/ fetal death occurred. See "Necropsy" under "F1 Generation." |
| Necropsy | No test article-related findings were noted. |

F1 Generation

| Parameter | Major Findings |
|---|---|
| Survival and birth examination | No test article related effects on survival were noted. No external morphological abnormalities were observed in any alive or dead (stillbirth) neonates. |
| Clinical signs | No test article-related clinical findings were noted. |
| Body weight | A slight decrease in gestation length resulting in a decrease in body weight of the neonates at birth observed at 100 mg/kg was considered nonadverse.<br>A possible test article-effect was noted for neonate birth weight in the 100 mg/kg/week group. Mean birth weight in the 100 mg/kg/week group was approximately 14 to 15% lower than the control group and was associated in many cases with a slightly reduced gestation length. It was considered that the average birth weight reduction was adequately explained by the slight decrease in gestation length, and in view of the fact that infants' growth after birth in this group was generally comparable with that of the control group infants, the biological significance of the intergroup differences in this study was considered uncertain and nonadverse, even if possibly CAT-354 related. Though the decreased mean group bodyweight trend continued until necropsy at PND 28 to 31 (approximately 14 to 15% lower than the control group), the weight gain and distribution of weight gains from birth to PND 28 to 31 necropsy were comparable amongst all groups. |
| Functional development | No test article-related changes were noted in any functional development parameters. |

| Parameter | Major Findings |
|---|---|
| Morphometric development | A decrease in head and chest circumference, and paw lengths, and a decrease in the absolute lung and spleen weights were considered reflective of the lower body weight observed in the 100 mg/kg group, supported by relative organ weights being comparable to those of the control group.<br>Morphological development parameters (body measurements) in the 100 mg/kg group were, in general, slightly smaller than those of the control group. Amongst these parameters, statistically significant decreases were noted in head circumference (184 vs. 200 [92%] in 100 mg/kg and control groups), chest circumference (126 vs. 146 [86%] in 100 mg/kg and control groups) and paw lengths (both right and left: 44 vs. 49 [90%] in 100 mg/kg and control groups) in the 100 mg/kg group. These changes were considered to be reflective of the lower neonate body weights (compared to controls) noted for this group at birth that continued until necropsy. |
| Skeletal evaluation | No test article-related skeletal findings were noted. |
| Ophthalmology | There were no test article-related ophthalmic findings. |
| Necropsy | No test article-related findings were noted. |
| Organ weights | A decrease in the absolute lung and spleen weights were considered reflective of the lower body weight observed in the 100 mg/kg group, supported by relative organ weights being comparable to those of the control group.<br>Neonate absolute organ weights in the 100 mg/kg group were decreased compared to control group for liver (males: 12.1106 vs. 12.7502, 95%; females: 9.2645 vs. 9.9338, 93%), lung (males: 4.7456 vs. 4.4969, 106%; females: 3.0996 vs. 3.5822, 87%), and spleen (males [two in total: 0.5922 g and 0.7890 g]: 0.6906 vs. 0.9468, 73%; females: 0.6006 vs. 0.7084, 85%). These changes were considered reflective of the lower body weight observed in this group, supported by relative organ weights being comparable to those of the control group.<br>Absolute and relative organ weights in the 30 mg/kg group were similar to those of the control group. |

**Study 2 Enhanced Pre-Postnatal Toxicity of CAT-354 Administered by Intravenous Infusion in Pregnant Cynomolgus Monkeys with 6-Month Postnatal Evaluation (Study #20054081)**

GLP compliance: Yes

*Key Study Findings*

- No test article-related adverse effects on maternal, fetal, or infant parameters.
- No test article-related effects on immune system parameters.
- No test article-related adverse macroscopic or microscopic findings were noted for the infants.
- The NOAEL for maternal and developmental toxicity was 100 mg/kg/week.
- The maternal GD 132 to 34 $C_{max}$ was 3940 μg/mL and $AUC_{0-7}$ was 20,300 μg day/mL.

*Methods*

| Parameter | Method Details |
|---|---|
| Dose and frequency of dosing: | 0 (vehicle), 30 and 100 mg/kg once a week from gestational day (GD)20 through natural delivery (approximately GD160) |
| Route of administration: | Intravenous |
| Formulation/vehicle: | Solution/ (b) (4) acetate, (b) (4) sodium chloride and (b) (4) polysorbate 80, pH 5.5 |
| Species/strain: | Monkeys/Cynomolgus monkeys (*Macaca fascicularis*) |
| Number/sex/group: | 20-22 females/group |
| Satellite groups: | None |
| Study design: | Pregnancy was determined by ultrasound monitoring and confirmed by monkey chorionic gonadotropin test when necessary. During gestation, the adult females were monitored for clinical signs (once daily) and changes in food consumption (once daily), body weight (at enrollment, GD25 and weekly thereafter until delivery), and pregnancy status, including embryo-fetal development status via ultrasound (biweekly). Blood samples from the adult females were collected at various time points throughout the study for clinical pathology, lymphocyte subset evaluation (flow cytometry), toxicokinetics, and antidrug antibody analyses. The pregnant females were allowed to deliver their infants by natural birth. For approximately 6 months postpartum/postnatal, the adult females and infants were evaluated for changes in clinical signs, body weight, and/or other parameters.<br>Infants underwent neurobehavioral assessments and skeletal evaluation within the first month. Blood samples from the infants were collected at various time points throughout the study for toxicokinetics and antidrug antibody formation analyses. Postnatal immunological assessments were conducted, including T-cell–dependent antibody response to keyhole limpet hemocyanin and lymphocyte subset evaluation (flow cytometry). The infants were euthanized on approximately birth day 180 (±2 days). An external and visceral exam and full necropsy were conducted on all infants, including macroscopic tissue examinations. A subset of tissues were collected, weighed, and preserved, and selected tissues were evaluated for histopathology. To the extent possible, infants were maintained with their mothers for the entire postnatal period, and mothers were released from the study once their infant was no longer on study. |
| Deviation from study protocol affecting interpretation of results: | None |

*Observations and Results*

F0 Dams

| Parameter | Major Findings |
|---|---|
| Mortality | No test article related effects on mortality were noted. |
| Clinical signs | No test article-related clinical findings were noted. |
| Body weight and food consumption | No test article-related effects on maternal body weight and food consumption were noted. |

| Parameter | Major Findings |
|---|---|
| Hematology and clinical chemistry | No test article related effects on hematology and clinical chemistry parameters were observed. |
| Necropsy findings<br>Cesarean section data | No test article-related findings were noted. No Cesarean section was performed for this study. |
| Immunology | There were no test article related changes in lymphocyte or monocyte cell populations. |

F1 Generation

| Parameter | Major Findings |
|---|---|
| Survival | No test article-related effects on survival were noted. |
| Clinical signs | No test article-related clinical findings were noted. |
| Body weights | No test article-related effects on body weight were noted. |
| External assessment and morphometric measurements | There were no test article-related alterations in external assessments or morphometric measurements. |
| Skeletal evaluations | No test article-related skeletal findings were noted. |
| Neurobehavioral assessment | No test article-related effects on the neurobehavioral evaluations were observed. |
| Ophthalmology | There were no test article-related ophthalmic findings. |
| Hematology and clinical chemistry | No test article related effects on hematology and clinical chemistry parameters were observed. |
| Necropsy | No test article-related findings were noted. |
| Organ weights | No test article-related effects on organ weights were observed. |
| Histopathology | No test article-related histopathologic findings were noted in the infants that died or were euthanized prior to scheduled necropsy. Potentially test article-related histiocytic infiltration of the spleen was considered nonadverse based on the nature of the change, incidence in control and treated animals, overall low incidence, and low severity. |
| Immunology | There were no test article-related changes in lymphocyte or monocyte cell populations and T-cell–dependent antibody response to keyhole limpet hemocyanin. |

## Juvenile Animal Toxicology Studies

No juvenile toxicology studies were conducted. An ePPND study was conducted in cynomolgus monkeys to assess the effects of tralokinumab on pre- and post-natal embryo-fetal development and infant development revealed no test article-related effects in infant monkeys up to 6 months of age (see above Study 2 under Prenatal and Postnatal Development). Tralokinumab was detected in the milk of lactating cynomolgus monkeys.

In addition, based on juvenile age range of 8 months to 3 years for cynomolgus monkeys, the juvenile phase was mostly covered by the repeat-dose studies in cynomolgus monkeys with approximate ages at start: 1.5 to 2.7 years in the 28-day intravenous study (Study #1348/053), 1.3 to 2.1 years in the 13-week intravenous study (Study #1348/058), 1.1 to 1.6 years in the 26-week intravenous study (Study #509615), and 1.5 to 2.4 years in the 13-week subcutaneous study (Study #514981).

Based on animal age and study findings in the repeat-dose toxicity studies and the ePPND study in monkeys, it has been determined that no additional juvenile animal toxicology studies are needed for this product.

## Other Toxicology/Specialized Studies

The code name for tralokinumab is CAT-354 in the studies outlined below.

**Study 1 Local Tolerance (Subcutaneous Injection) of CAT-354 in Rabbits (Study #513286, GLP)**

In a local tolerance study (Study #513286), six male New Zealand white rabbits received a single SC administration of 0.3, 0.5, or 1.0 mL of vehicle control (b) (4) sodium acetate, (b) (4) sodium chloride, (b) (4) polysorbate 80, pH 5.5) or tralokinumab at 150 mg/mL (corresponding to , 75, or 150 mg/injection; i.e., 15, 25, or 50 mg/kg for a 3 kg rabbit) at six separate sites. Three animals were sacrificed 2 days (Day 3) after dosing, with the remaining three animals sacrificed on Day 7 after an additional 4 days of observation.

All animals survived until scheduled necropsy. No tralokinumab-related clinical signs and no tralokinumab-related effects on body weight were noted. There were no visible and histological signs of local toxicity at the injection sites. Therefore, tralokinumab was not toxic locally at the subcutaneous site of administration.

Local tolerance was also assessed as part of the repeat-dose studies conducted in cynomolgus monkeys up to 26 weeks (IV) or 13 weeks (SC). No tralokinumab-related adverse findings were noted at the injection sites in cynomolgus monkeys in the repeat-dose studies at doses up to 100 mg/kg IV or up to 300 mg/injection SC.

**Study 2 CAT-354: An Immunohistochemical Investigation of Cross-Reactivity in Human Tissues (Study #CAT-354 Rp014, GLP)**

CAT-354 was conjugated to fluorescein isothiocyanate (CAT-354-FITC) to determine whether it binds with human tissues. CAT-354-FITC was incubated at concentrations of 100, 250, and 500 ng/mL for 60 min with 37 different tissues obtained from three donors. The positive control was tissue blocks of cardiac muscle containing IL-13–coated Sepharose beads embedded in optimum cutting temperature compound and the negative control contained bovine serum albumin-coated Sepharose beads embedded in optimum cutting temperature compound. Following staining, the localization of CAT-354 was evaluated by light microscopy. The results were subjected to a peer review.

Results: There was no cross-reactivity of CAT-354 in human tissues.

Conclusion: CAT-354 did not cross-react in human tissues.

### 13.1.5. Excipients / Impurities

Tralokinumab injection does not contain novel excipients or excipients of human or animal origin.

None of the impurities in the biologic product cause safety concerns. Refer to Section II.9 for details. The Applicant provided an overview of the drug substance batches used in the

nonclinical safety studies. The batches used for nonclinical testing are considered representative of the clinical batches used. Justification of specification for (b) (4) impurities for tralokinumab was provided. The chronic toxicology study supports the safety of human exposure to tralokinumab fragments and total impurity exposure at the proposed drug product stability release limit.

**Table 47. Safety Margins for Tralokinumab Total Impurities by Nonreducing Gel Electrophoresis**

| Toxicology Study | Tralokinumab Toxicology Lot | % Estimated Total Impurities in Toxicology Lot (accounting for maximum observed half antibody) | Total Impurities per Dosing Interval at NOAEL[a] (mg/kg/6 months) | End of shelf life Drug Product Total Impurities Limit [b] | Maximum Total Impurities per initial 600 mg dose followed by 300 mg dose every second week per 26 weeks [c] | Margin based on Initial 26-week Dosing Interval [d] |
|---|---|---|---|---|---|---|
| 26-week IV study in cynomolgus monkeys (509615) | P241420 | (b) (4) | | | | |
| | 34789 | | | | | |

NOAEL = no-observed-adverse-effect level

[a] NOAEL = 100 mg/kg (once weekly dosing for 26 weeks)
[b] Based on maximum acceptance criteria for drug product stability
[c] Based on 60 kg subject
[d] Based on mg/kg dose comparison, with 600 mg initial dose followed by 300 mg dose every second week (1 600 mg dose and 13 300 mg doses over 26 weeks)

Source: BLA 761180, Section 3.2.S.4.5 Justification of Specification(s).
Abbreviation: IV, intravenous

**Table 48. Safety Margins for Tralokinumab Total Impurities by Reducing Gel Electrophoresis**

| Toxicology Study | Tralokinumab Toxicology Lot | % Total Impurities in Toxicology Lot | Total Impurities per Dosing Interval at NOAEL[a] (mg/kg/26 weeks) | End of shelf life Drug Product Total Impurities Limit [b] | Maximum Total Impurities per initial 600 mg dose followed by 300 mg dose every second week per 26 weeks [c] | Margin based on Initial 26-week Dosing Interval [d] |
|---|---|---|---|---|---|---|
| 26-week IV study in cynomolgus monkeys (509615) | P241420 | (b) (4) | | | | |
| | 34789 | | | | | |

NOAEL = no-observed-adverse-effect level

[a] NOAEL = 100 mg/kg (once weekly dosing for 26 weeks)

[b] Based on maximum acceptance criteria for drug product stability

[c] Based on 60 kg subject

[d] Based on mg/kg dose comparison, with 600 mg initial dose followed by 300 mg dose every second week (1 600 mg dose and 13 300 mg doses over 26 weeks)

Source: BLA 761180, Section 3.2.S.4.5 Justification of Specification(s).
Abbreviation: IV, intravenous

**Table 49. Safety Margins for Tralokinumab Aggregates by HPSEC**

| Toxicology Study | Tralokinumab Toxicology Lot | % Aggregates in Toxicology Lot | Aggregates per Dosing Interval at NOAEL[a] (mg/kg/26 weeks) | End of Shelf Life Drug Product Aggregates Limit[b] | Maximum Aggregates per Initial 600 mg Dose Followed by 300 mg Dose Every Second Week per 26 Weeks[c] | Margin Based on Initial 26-Week Dosing Interval[d] |
|---|---|---|---|---|---|---|
| 26-week IV study in cynomolgus monkeys (509615) | P241420 | (b) (4) | | | | |
| | 34789 | | | | | |

NOAEL = no-observed-adverse-effect level

[a] NOAEL = 100 mg/kg (once weekly dosing for 26 weeks)

[b] Based on maximum acceptance criteria for drug product stability

[c] Based on 60 kg subject

[d] Based on mg/kg dose comparison, with 600 mg initial dose followed by 300 mg dose every second week (1 600 mg dose and 13 300 mg doses over 26 weeks)

Source: BLA 761180, Section 3.2.S.4.5 Justification of Specification(s).
Abbreviation: HPSEC, high performance size exclusion chromatography; IV, intravenous

### 13.1.6. Extractables/Leachables

The primary container closure system for Drug Substance is the [redacted] Following a review of the potential extractables list from [redacted] the safety of the drug substance storage container was evaluated based on a three-stage, risk-based strategy: [redacted] An assessment with experimental studies was performed at each stage. The analytical methods used in the [redacted] extractables and leachables studies were selected to monitor volatile compounds, semivolatile compounds, nonvolatile compounds, and elements. The Applicant proposes that the acceptable intake from individual impurities be set at [redacted] µg/day [redacted] µg/dose). The recommended clinical dose is an initial dose of 600 mg, followed by 300 mg Q2W. Therefore, the proposed acceptable intake from individual impurities of [redacted] µg/dose is acceptable from a pharmacology/toxicology perspective based on the proposed dosage regimen and ICH M7 (R1): Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk. There are no safety concerns with the extractables and leachables impurities based on the results from [redacted] drug substance extractables and leachables studies and the drug product leachables and elemental impurities testing. Refer to Section 13.2. for details.

### 13.1.7. Referenced NDAs, BLAs, Drug Master Files

This BLA makes reference to the following MFs:

[redacted]

## 13.2. Individual Reviews of Studies Submitted to the NDA

### 13.2.1. Pharmacology

Four pharmacology studies were included in the BLA submission that were not submitted to the IND previously. The code name for tralokinumab is CAT-354. A summary of those studies is provided below.

Tralokinumab had a strong affinity for human IL-13($K_D$ 58pM) and dose-dependently prevented IL-13 from interacting with IL-13Rα1 and IL-13Rα2 (Study #RIA354-049 Popovic2017).

Tralokinumab dose-dependently inhibited gene expression of CCL2 ($IC_{50}$ 201pM), CCL26 ($IC_{50}$ 189pM), NTRK1 ($IC_{50}$ 268pM) and IL13RA2 ($IC_{50}$ 367pM) as well as secretion of CCL-2/MCP-1 ($IC_{50}$ 217pM) induced by IL-13 but not IL-4 in human epidermal keratinocytes (Study #REP-HND-2019-02).

Tralokinumab dose-dependently inhibited downregulation of FLG ($IC_{50}$ 19.1nM), FLG2 ($IC_{50}$ 16.4nM), LOR ($IC_{50}$ 16.0 and 13.3nM), ELOVL3 ($IC_{50}$ 16.2nM) and DEFB4A ($IC_{50}$ 13.0nM) mediated by IL-13 but not IL-4 in human epidermal keratinocytes (Study #REP-HND-2019-03).

Tralokinumab dose-dependently inhibited gene expression of CCL2 ($IC_{50}$ 315pM), CCL11 ($IC_{50}$ 112pM), and POSTN ($IC_{50}$ 241pM), as well as secretion of CCL-2/MCP-1 ($IC_{50}$ 336pM) induced by IL-13 but not by IL-4 in human dermal fibroblasts (Study #REP-HND-2019-04).

## 13.2.2. Extractables/Leachables

### Description of Container Closure System for Drug Substance

The primary container closure system for Drug Substance is (b) (4)

**Table 50. (b) (4) Materials of Construction**

| Component | Material | Drug Master File Number |
|---|---|---|
| (b) (4) | | |

Source: BLA 761180, Section 3.2.S.6 Container Closure System.

The Drug Substance fill target (b) (4)

**Strategy for Extractables and Leachables Studies**

Following a review of the potential extractables list from (b) (4) the safety of the Drug Substance storage container was evaluated (b) (4) (Figure 28).

**Figure 28. Strategy for Leachables and Extractables Studies**

(b) (4)

Source: BLA 761180, Section 3.2.S.6 Container Closure System.

These studies were performed to ensure that the product contact components do not leach undesirable amounts of potentially harmful compounds into the Drug Substance that may adversely impact patient safety. (b) (4)

## The Threshold of Toxicological Concern and Analytical Methods

The analytical methods used in (b) (4) extractables and leachables studies were selected (b) (4) The methods and reporting limits are provided in Table 51.

**Table 51. (b) (4) Extractables and Leachables Methods**

| Method | Species Detected | Reporting Limit (µg/mL [a]) |
|---|---|---|
| (b) (4) | (b) (4) | (b) (4) |
| (b) (4) | | |

b Reporting limits are defined based on the method standard which contained all reported elements.
Source: BLA 761180, Section 3.2.S.6 Container Closure System.

The reporting limits are suitable to identify species at a level more sensitive than the threshold of toxicological concern for genotoxic impurities described in ICH M7 (R1): *Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk.*

The Applicant proposes that the acceptable intake from individual impurities is set at (b) (4) µg/day (b) (4) µg/dose). The recommended clinical dose is an initial dose of 600 mg, followed by 300 mg Q2W. Therefore, the proposed acceptable intake from individual impurities of (b) (4) µg/dose is acceptable from a Pharmacology/Toxicology perspective based on the propose osage regimen and ICH M7 (R1): *Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk.*

(b) (4)



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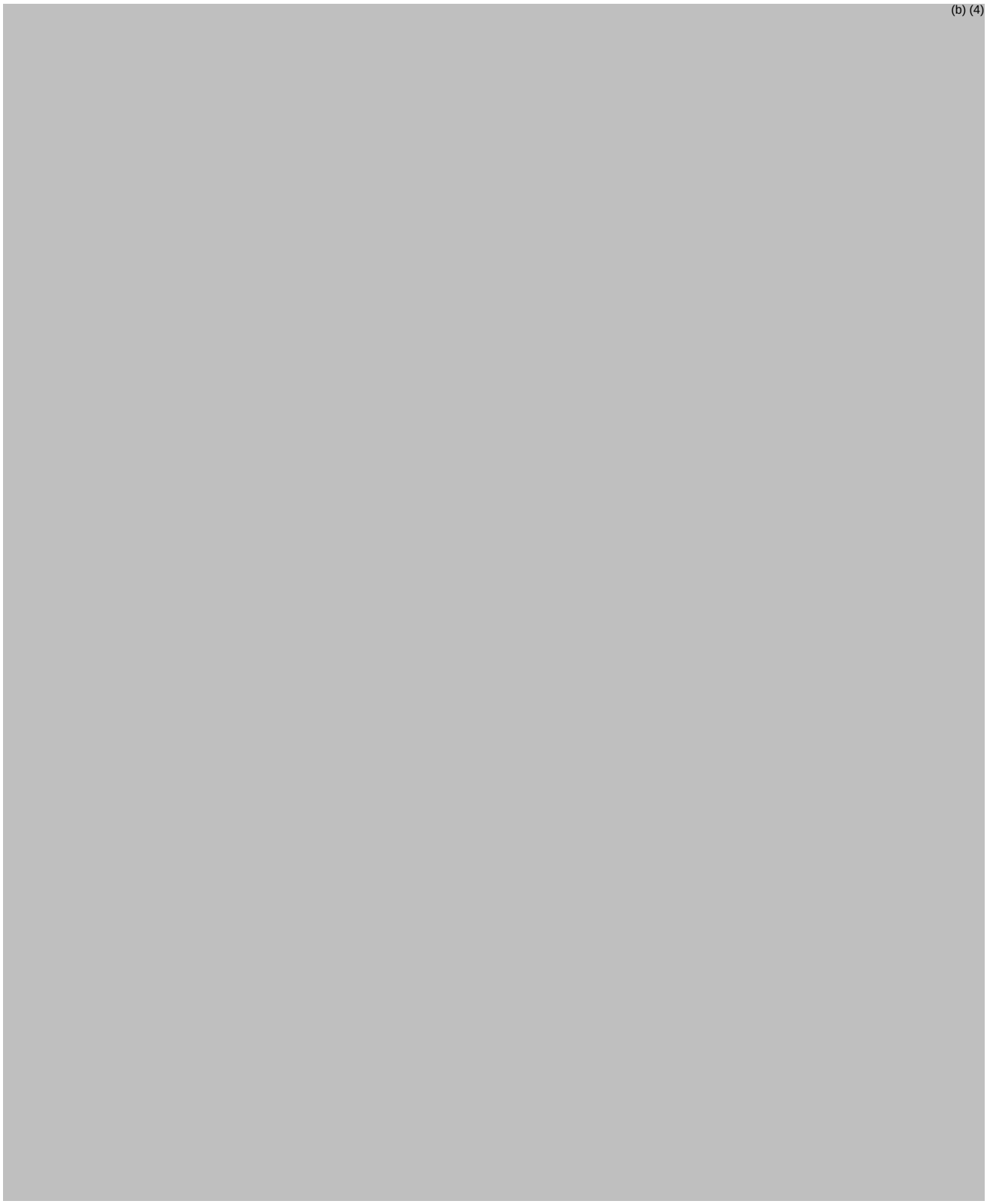
**Container Closure System for Drug Product**

(b) (4)



(b) (4)

## 13.3. Labeling

(b) (4)


## Recommended Revision to the Nonclinical Portions of Labeling

Revisions to the Applicant's proposed wording for the nonclinical and related sections of the label are provided below. It is recommended that the underlined wording be inserted into and the ~~struckthrough~~ wording be deleted from the text of the (b) (4) label.

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

**INDICATIONS AND USAGE**

(b) (4) is an interleukin-13 antagonist indicated for the treatment of ….

**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy**

Risk Summary

There is limited data from the use of (b) (4) in pregnant women to inform a drug-associated risk of adverse developmental outcomes. Human IgG antibodies are known to cross the placental barrier; therefore, (b) (4) may be transmitted from the mother to the developing fetus.

In (b) (4) an enhanced pre- and post-natal developmental studies, no adverse developmental effects were observed in offspring born to pregnant monkeys after (b) (4) intravenous administration of (b) (4) tralokinumab during organogenesis through parturition at doses up to 10 times the maximum recommended human dose (MRHD) (*see Data*).

The (b) (4) background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

*Animal Data*

In a pre- and post-natal development study, intravenous doses up to 100 mg/kg tralokinumab were administered to pregnant cynomolgus monkeys once every week from gestation day 20 to parturition. No maternal or developmental toxicity was observed at doses up to 100 mg/kg/week (10 times the MRHD on a mg/kg basis of 10 mg/kg/week).

In an enhanced pre- and post-natal development study, intravenous doses up to 100 mg/kg tralokinumab (10 times the MRHD on a mg/kg basis of 10 mg/kg/week) were administered to pregnant cynomolgus monkeys once every week from the beginning of organogenesis to parturition. (b) (4) . No treatment-related adverse effects on embryofetal toxicity or malformations, or on morphological, functional, or immunological development were observed in the infants from birth through 6 months of age.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Tralokinumab is a (b) (4) human IgG4 monoclonal antibody that specifically binds to human (b) (4) interleukin-13 (IL-13) and inhibits its interaction with the IL-13 receptor α1 and α2 subunits (IL-13Rα1 and IL-13Rα2) (b) (4) IL- 13 is a naturally occurring cytokine of the Type 2 immune response. Tralokinumab inhibits the bioactivity of IL- 13 by blocking IL-13 interaction with IL-13Rα1/IL-4Rα receptor complex. Tralokinumab inhibits IL-13-induced responses including the release of proinflammatory cytokines, chemokines and IgE.

(b) (4)

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4)

Animal (b) (4) studies have not been conducted to evaluate (b) (4) tralokinumab. An evaluation of the available evidence related to IL-13 inhibition and animal toxicology data with tralokinumab does not suggest an increased carcinogenic or mutagenic potential of for tralokinumab.

(b) (4)

(b) (4)

No effects on fertility parameters such as reproductive organs, menstrual cycle and sperm analysis were observed in male or female sexually mature cynomolgus monkeys that were subcutaneously administered tralokinumab treated subcutaneously with tralokinumab at doses up to 350 mg/animal (10 times the MRHD on a mg/kg basis of 10 mg/kg/week) in (females) once a week for three consecutive menstrual cycles (maximum of 15 doses) or 600 mg/animal (10 times

the MRHD on a mg/kg basis of 10 mg/kg/week) in (males) once a week for 13 weeks. The monkeys were not mated to evaluate fertility.

**Clean version of the recommended nonclinical portions of labeling**

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

**INDICATIONS AND USAGE**

(b) (4) is an interleukin-13 antagonist indicated for ….

**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy**

Risk Summary

There is limited data from the use of (b) (4) in pregnant women to inform a drug-associated risk of adverse developmental outcomes. Human IgG antibodies are known to cross the placental barrier; therefore, (b) (4) may be transmitted from the mother to the developing fetus.

In an enhanced pre- and post-natal development study, no adverse developmental effects were observed in offspring born to pregnant monkeys after intravenous administration of tralokinumab during organogenesis through parturition at doses up to 10 times the maximum recommended human dose (MRHD) (b) (4)

The (b) (4) background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

*Animal Data*

In a pre- and post-natal development study, intravenous doses up to 100 mg/kg tralokinumab were administered to pregnant cynomolgus monkeys once every week from gestation day 20 to parturition. No maternal or developmental toxicity was observed at doses up to 100 mg/kg/week (10 times the MRHD on a mg/kg basis of 10 mg/kg/week).

In an enhanced pre- and post-natal development study, intravenous doses up to 100 mg/kg tralokinumab (10 times the MRHD on a mg/kg basis of 10 mg/kg/week) were administered to pregnant cynomolgus monkeys once every week from the beginning of organogenesis to parturition. No treatment-related adverse effects on embryofetal toxicity or malformations, or on morphological, functional, or immunological development were observed in the infants from birth through 6 months of age.

**12 CLINICAL PHARMACOLOGY**

**12.1 Mechanism of Action**

Tralokinumab is a human IgG4 monoclonal antibody that specifically binds to human interleukin-13 (IL-13) and inhibits its interaction with the IL-13 receptor α1 and α2 subunits (IL-

13Rα1 and IL-13Rα2). IL-13 is a naturally occurring cytokine of the Type 2 immune response. Tralokinumab inhibits the bioactivity of IL-13 by blocking IL-13 interaction with IL-13Rα1/IL-4Rα receptor complex. Tralokinumab inhibits IL-13-induced responses including the release of proinflammatory cytokines, chemokines and IgE.

**13 NONCLINICAL TOXICOLOGY**

**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

Animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of tralokinumab.

No effects on fertility parameters such as reproductive organs, menstrual cycle and sperm analysis were observed in male or female sexually mature cynomolgus monkeys that were subcutaneously administered tralokinumab at doses up to 350 mg/animal (10 times the MRHD on a mg/kg basis of 10 mg/kg/week) in females once a week for three consecutive menstrual cycles (maximum of 15 doses) or 600 mg/animal (10 times the MRHD on a mg/kg basis of 10 mg/kg/week) in males once a week for 13 weeks. The monkeys were not mated to evaluate fertility.

# 14. Clinical Pharmacology: Additional Information and Assessment

## 14.1. Individual Study Review

### 14.1.1. Summary of Bioanalytical Method Validation and Performance of the Assays for Measuring Tralokinumab Serum Concentrations

In the Phase 1 trial CAT-354-0401 (asthma), tralokinumab serum concentrations were measured by enzyme-linked immunosorbent assay. Tralokinumab in serum samples and standards was bound to immobilized IL-13 antigen and detected using a horseradish peroxidase-linked sheep polyclonal antibody specific for human IgG4.

The assay was validated for determination of tralokinumab in human serum by establishing the following validation parameters: accuracy, precision, specificity, and linearity. Standards of tralokinumab were prepared in 20% control serum. Serum samples were diluted five-fold prior to analysis and further diluted in 20% control serum as necessary to fall within the linear range of the assay. Samples, standards, and controls were analyzed in duplicate. A 4-parameter fit was used to model the standard curve.

In all trials other than CAT-354-0401, tralokinumab serum concentrations were measured using a validated sandwich assay on the Gyrolab® platform. Standards of tralokinumab were prepared in neat human serum (undiluted control serum). Serum samples were diluted in neat serum as necessary to fall within the linear range of the standard curve. Samples, standards, and controls were diluted 20-fold prior to analysis and were analyzed in duplicate. A 5-parameter fit was used to model the standard curve.

The assay was initially validated by MedImmune Ltd. The assay was subsequently transferred to (b) (4) Interlaboratory test sample results were comparable throughout the validated assay range. Furthermore, the assay was revalidated at (b) (4). before being used in the ECZTRA trials in order to re-establish the assay with new labeled reagents and to assess the assay selectivity and the long-term stability of tralokinumab in the serum of subjects with AD.

Overall, the bioanalytical method for measuring serum tralokinumab concentrations is considered acceptable (Table 57).

**Table 57. Summary of Method Validation Parameters for Bioanalytical Assays for Measurement of Tralokinumab Concentrations in Human Plasma**

| | | | |
|---|---|---|---|
| **Bioanalytical method validation report name, amendments, and hyperlinks** | Method validation for the determination of tralokinumab in human serum using the Gyrolab platform<br>Report 8295601: M5.3.1.4 8295601<br>Report 8362751: M5.3.1.4 8362751<br>Report 8361001: M5.3.1.4 8361001<br>Report 8362755: M5.3.1.4 8362755<br>Report 8362717: M5.3.5.1 Bioanalytical report<br>Report (b) (4) 111653 (b) (4)<br>M5.3.5.4 CD-RI-CAT-354-1049 Analytical Report (b) (4) 111653 (b) (4)<br>Report (b) (4) 100911/2: M5.3.1.4 (b) (4) 100911/2 | | |
| **Method description** | A sandwich immunoassay using biotinylated tralokinumab anti-idiotype capture antibody and Alexa Fluor 647-labelled sheep polyclonal antibody specific to human IgG4 for detection. Alexa Fluor 647 fluorescence was detected using a laser-induced fluorescence detector within the Gyrolab instrument. | | |
| **Materials used for standard calibration curve and concentration** | • Tralokinumab (150 mg/mL), lot 007C15A – Study 8362751.<br>• Tralokinumab (52.5 mg/mL), lot RSN35411G – Study 8295601.<br>• Tralokinumab (51.4 mg/mL), lot CAT-354-WR5354-1-352838 – Study 8361001. | | |
| **Validated assay range** | 0.100 to 40.0 µg/mL | | |
| **Material used for quality controls (QCs) and concentration** | • Tralokinumab (150 mg/mL), lot 007C15A; – (b) (4) Studies 8362751, 8362755, 8362717 (ECZTRA 1), 8362722 (ECZTRA 2), 8377444 (ECZTRA 3), and 8391819 (ECZTRA 5).<br>• Tralokinumab (52.5 mg/mL), lot RSN35411G – (b) (4) Studies 8295601 and 8321336 (D2213C00001).<br>• Tralokinumab (51.4 mg/mL), lot CAT-354-WR5354-1-352838 – (b) (4) Study 8361001. | | |
| **Minimum required dilutions (MRDs)** | 1 in 20 | | |
| **Source and lot of reagents** | • Tralokinumab (150 mg/mL), lot 007C15A, provided by LEO (b) (4)<br>• Tralokinumab (52.5 mg/mL), lot RSN35411G, provided by MedImmune.<br>• Tralokinumab (51.4 mg/mL), lot CAT-354-WR5354-1-352838, provided by MedImmune. | | |
| **Regression model and weighting** | 5-parametric regression, $1/Y^2$ weighting | | |
| **Validation parameters** | **Method validation summary** | | **Source location** |
| **Standard calibration curve performance during accuracy and precision runs** | Number of standard calibrators from LLOQ to ULOQ | 7 | Table 1 of Report 8362751 |
| | Cumulative accuracy (%bias) from LLOQ to ULOQ | | |
| | Tralokinumab, Study 8362751 | -1.7 to 3.0% | Derived from Table 1 of Report 8362751 |
| | Tralokinumab, Study 8295601 | -0.8 to 2.0% | Appendix 2 Table 1 of Report 8295601 |
| | Cumulative precision (%CV) from LLOQ to ULOQ | | |
| | Tralokinumab, Study 8362751 | ≤ 8.2% | Derived from Table 1 of Report 8362751 |
| | Tralokinumab, Study 8295601 | ≤ 5.0% | Appendix 2 Table 1 of Report 8295601 |

| | | | |
|---|---|---|---|
| **Performance of QCs during accuracy and precision runs** | **Cumulative accuracy (%bias) in 5 QCs** | | Tables 3 and 4 of Report 8362751 |
| | QCs for Tralokinumab, Study 8362751 | 1.0 to 8.0% | |
| | QCs for Tralokinumab, Study 8295601 | -9.5 to – 4.1% | Appendix 2 Table 3 of Report 8295601 |
| | **Inter-batch %CV** | | Tables 3 and 4 of Report 8362751 |
| | QCs for tralokinumab, Study 8362751 | ≤ 15.4% | |
| | QCs for tralokinumab, Study 8295601 | ≤ 11.0% | Appendix 2 Table 3 of Report 8295601 |
| | **Total error (TE)** | | Tables 3 and 4 of Report 8362751 |
| | QCs for tralokinumab, Study 8362751 | ≤ 21.8% | |
| | QCs for tralokinumab, Study 8295601 | ≤ 20.5% | Appendix 2 Table 3 of Report 8295601 |
| **Selectivity & matrix effect in disease state (atopic dermatitis) serum** | 10 of 10 (100%) unspiked lots generated a result less than the LLOQ<br>9 of 10 (90%) lots met criteria at the LLOQ with %bias ranging from -8.9 to 30 and 9 of 10 (90%) lots met criteria at the HQC with %bias ranging from -0.3 to 32.8. | | Table 6 of Report 8362751 |
| **Interference & specificity** | NA | | NA |
| **Haemolysis effect** | NA | | NA |
| **Lipemic effect** | 3 of 3 lots met criteria at LQC at HQC levels with % bias from -14.6 to 3.1%. | | Appendix 2 Tables 13, 14, and 15 of Report 8295601 |
| **Dilution linearity & hook effect** | • Up to 4000 µg/mL and up to 1 in 15625 dilution (in addition to the MRD) was deemed acceptable with a % bias of -2.3 to 16.5%.<br>• No hook effect was observed. | | Appendix 2 Table 11 of Report 8295601 |
| **Bench-top/process stability** | 24 hours at room temperature. | | Appendix 2 Table 18 of Report 8295601 |
| | Diluted samples may be stored in refrigerator up to 5 days prior to analysis | | Section 12.1 Tables 7 and 8 of Report 8361001 |
| **Freeze-thaw stability** | 6 cycles at <50°C, tralokinumab in normal serum | | Appendix 2 Table 17 of Report 8295601 |
| | 9 cycles at <-50°C, tralokinumab in normal serum | | Section 20.5 Table 4 of Report 8362717 |
| **Long-term storage** | 611 days at <-50°C, tralokinumab in atopic dermatitis serum** | | Section 11.6 Table 6 of Report 8362755 |
| | 660 days at nominal -80°C, tralokinumab in normal serum | | Table 8 of Report QBR111653QB03 |
| | 186 days at <-20°C, tralokinumab in normal serum | | Section 9 Table 17 of Report HFL100911/2 |
| **Parallelism** | NA | | NA |
| **Carry-over** | NA | | NA |

Source: Appendix 2, 2.7.1 Summary of biopharmaceutics and associated analytical methods
Abbreviations: CV, coefficient of variation; ECZTRA, ECZema TRAlokinumab; HQC, high quality control; LLOQ, lower limit of quantification; LQC, low quality control; MRD, maximum recommended dose; NA, not applicable; ULOQ, upper limit of quantification

## 14.1.2. Study CAT-354-0703

### Title

An Open-Label, Parallel-Group, Bioavailability Study to Assess the Pharmacokinetics of CAT-354 Following Subcutaneous and Intravenous Administration

### Objectives

The primary objective was to compare CAT-354 bioavailability following SC administration of 150 mg and 300 mg CAT-354 compared to 150 mg CAT-354 IV administration.

The secondary objectives were to assess other PK parameters, and the safety and tolerability of SC administration of CAT-354.

### Trial Design

This was a randomized, open-label, parallel-group, single-dose trial in healthy men, conducted at a single site in the United States. Subjects were randomized in a 1:1:1 ratio to a single dose of tralokinumab 150 mg via a 30 min IV infusion or tralokinumab 150 mg or 300 mg via SC injection. Subjects were followed up for at least 8 weeks postdose for assessment of PK, safety, and immunogenicity.

Blood samples for PK assessment were collected over the first 24 hr (immediately predose and postinfusion; 0.5, 1, 3, 8, and 24 hr postdose), then on Days 3, 5, 7, and 9, and Weeks 2, 3, 4, 5, 6, and 8 postdose.

#### Subject Disposition and Baseline Demographics

A total of 30 subjects was randomized and received their planned tralokinumab dose. Twenty-nine subjects (96.7%) completed the trial. The remaining subject (who received tralokinumab 300 mg SC) was lost to follow-up, but provided sufficient data to be included in the PK and safety analysis populations.

The demographic data were similar across treatment groups except for body weight (Table 58). All subjects were male, and the majority were white and not Hispanic or Latino. The mean age was 32.5 years (SD 10.1, range 20 to 54 years), the mean body weight was 83.7 kg (SD 12.1, range 59 to 109 kg), and the mean body mass index (BMI) was 25.8 kg/$m^2$ (SD 3.0, range 19.8 to 30.0 kg/$m^2$).

**Table 58. Subject Body Weight at Baseline (Trial CAT-354-0703)**

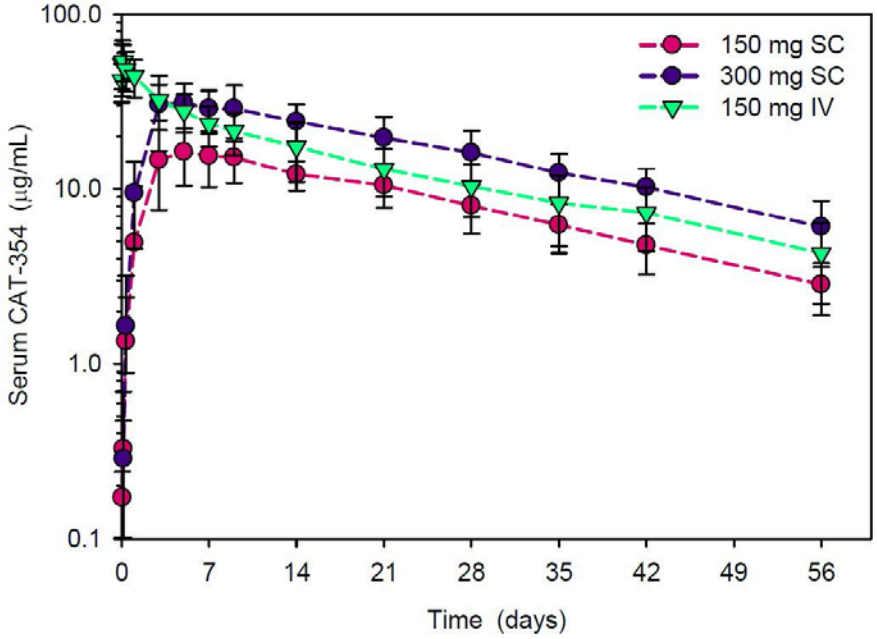
| Body weight (kg) | Tralokinumab dose group | | |
|---|---|---|---|
| | 150 mg IV (N=10) | 150 mg SC (N=10) | 300 mg SC (N=10) |
| Mean (SD) | 78.7 (14.7) | 87.3 (8.1) | 85.3 (12.2) |
| Range | 59.0–109 | 74.8–98.4 | 68.0–102 |

Source: Panel 2. 2.7.2 Summary of Clinical Pharmacology Studies.
Abbreviations: IV, intravenous; N, number of subjects; SC, subcutaneous; SD, standard deviation

## Pharmacokinetic Results

The mean concentration-time profile for tralokinumab is shown in Figure 29.

**Figure 29. Mean Tralokinumab Concentration-Time Profile After Single Intravenous and Subcutaneous Doses (Trial CAT-354-0703)**




Source: Panel 3. 2.7.2 Summary of Clinical Pharmacology Studies.
The concentration–time profile is shown as mean±standard deviation on a $\log_{10}$ scale.
Abbreviations: CAT-354, tralokinumab; IV, intravenous; SC, subcutaneous

The absolute bioavailability of tralokinumab after SC injection calculated by comparing the $AUC_{0-\infty}$ values after a single SC dose versus a single IV dose was 62% (90% CI 48.5 to 79.6) for the 150 mg dose and 60% (90% CI 46.9 to 77.1) for the 300 mg dose.

The key PK parameters for tralokinumab are shown in Table 59. There was a dose-proportional increase in systemic drug exposure, as assessed by $C_{max}$ and AUC, from the 150 mg to the 300 mg dose group. The mean t½ and clearance (CL) were similar after both SC doses and the IV dose.

**Table 59. Pharmacokinetic Parameters for Tralokinumab After Single Intravenous and Subcutaneous Doses (Trial CAT-354-0703)**

| Parameter | Tralokinumab dose group | | |
|---|---|---|---|
| | 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 |
| Cmax, 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 |
| Tmax (min, max), days | 0.06 (0.04, 1.02) | 5 (3, 9) | 5 (3, 9) |
| t½, days | 21.4 ± 2.5 | 19.2 ± 3.1 | 19.4 ± 3.6 |
| Vd, mL/kg | 63.6 ± 16.6 | ND | ND |

Source: Panel 4. 2.7.2 Summary of Clinical Pharmacology Studies.
Abbreviations: $AUC_{0-\infty}$, area under the concentration–time curve from time 0 to infinity; $C_L$, clearance, $C_{L/F}$, clearance after oral administration; $C_{max}$, maximum concentration; IV, intravenous; SC, subcutaneous; $t_{1/2}$, terminal half-life; $T_{max}$, time to $C_{max}$, $V_d$, volume of distribution

## Safety Results

The tralokinumab doses administered in this trial were well tolerated, and no safety concerns were identified. No ADAs were detected in any subject.

***Reviewer's Comments***

(1) *In the SC dose range of 150 mg to 300 mg, tralokinumab systemic drug exposure was demonstrated to be dose-proportional, as assessed by $C_{max}$ and AUC.*
(2) *The mean $t_{½}$ and CL were similar after both SC and IV drug administration.*
(3) *The bioavailability might be underestimated, given the mean body weight was higher for subjects in the SC groups than for subjects in the IV group (Table 59), and that exposure of tralokinumab decreases with increasing body weight. Of note, the bioavailability was estimated to be 76% in the popPK analysis.*

# 14.1.3. Study MI-CP224

## Title

A Phase 1, Single-Center, Single-Blind, Randomized, Placebo-Controlled, Single Ascending Dose Study to Assess the Safety, Tolerability, Pharmacokinetics and Immunogenicity of CAT-354 Following Subcutaneous Administration in Healthy Male and Female Japanese Subjects

## Objectives

The primary objective of this study was to assess the safety and tolerability of SC administration of CAT-354 in healthy Japanese subjects.

The secondary objective of this study was to assess the pharmacokinetics and immunogenicity of SC administration of CAT-354 in healthy Japanese subjects.

## Trial Design

This was a randomized, single-blind, placebo-controlled, single ascending dose trial in healthy Japanese men and women, conducted at a single site in the United States.

Three dose levels of tralokinumab (150 mg, 300 mg, and 600 mg) were studied in three sequential dose cohorts. Within each dose cohort, subjects were randomized in an 8:2 ratio to a single SC dose of tralokinumab or placebo. Subjects were followed up for 10 weeks postdose for assessment of PK, safety, and immunogenicity.

Blood samples for PK assessment were collected over the first 24 hr (predose; 0.5, 1, 3, 8, and 24 hr postdose), then on Days 3, 5, 7, and 9, and Weeks 2, 3, 4, 5, 6, 8, and 10 postdose.

### Subject Disposition and Baseline Demographics

A total of 30 subjects was randomized (10 per cohort) and all received their planned tralokinumab dose. All subjects completed the trial.

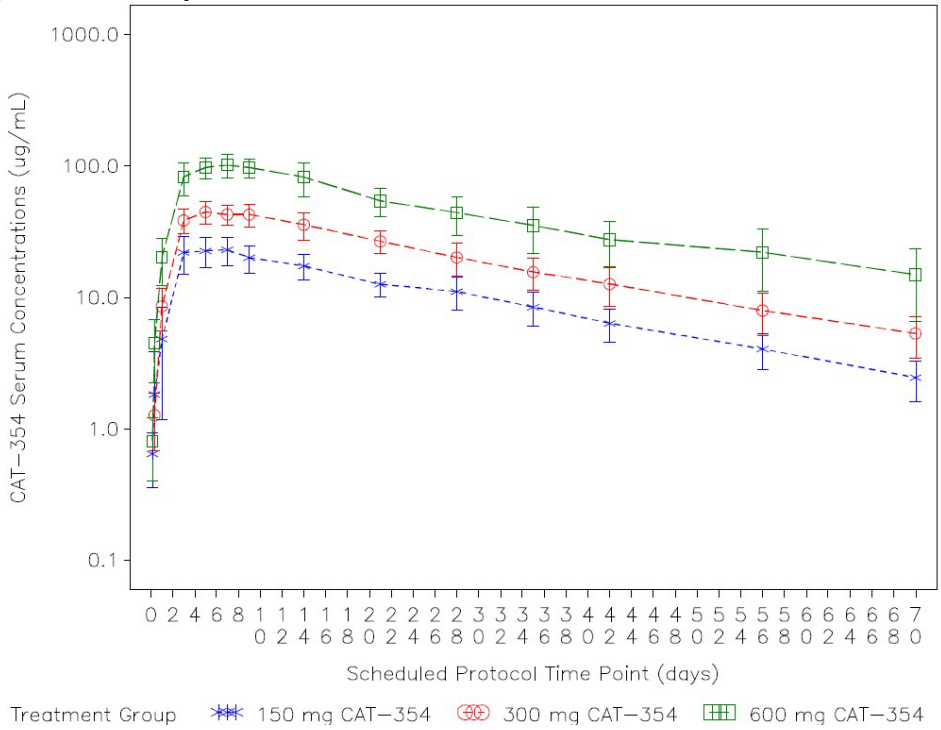
All subjects were Japanese, 60% were male, and 40% were female. Each treatment group enrolled at least 25% female subjects. The demographic data were comparable across treatment

groups. The mean age was 33.6 years (SD 9.7, range 22 to 52 years), the mean body weight was 61.5 kg (SD 8.6, range 45 to 77 kg), and the mean BMI was 21.7 kg/m$^2$ (SD 2.1, range 18.0 to 25.7 kg/m$^2$).

## Pharmacokinetic Results

The mean concentration-time profile for tralokinumab is shown in Figure 30.

**Figure 30. Mean Tralokinumab Concentration-Time Profile After a Single Subcutaneous Dose (Trial MI-CP224)**




Source: Panel 5. 2.7.2 Summary of Clinical Pharmacology Studies.
The concentration–time profile is shown as mean±standard deviation on a $\log_{10}$ scale.
Abbreviation: CAT-354, tralokinumab

The key PK parameters for tralokinumab are shown in Table 60. Systemic exposure to tralokinumab, as assessed by $C_{max}$ and AUC, increased in a dose-proportional manner. The dose proportionality was confirmed by statistical analysis. The point estimate of the slope was close to 1.0 for each parameter (1.06 for $C_{max}$, 1.08 for $AUC_{0-t}$, and 1.12 for $AUC_{0-\infty}$) and the 90% CIs included the value of 1.

**Table 60. Pharmacokinetic Parameters for Tralokinumab After a Single Subcutaneous Dose (Trial MI-CP224)**

| Parameter | Tralokinumab dose group | | |
|---|---|---|---|
| | 150 mg (N=8) | 300 mg (N=8) | 600 mg (N=8) |
| $AUC_{0-\infty}$, µg×day/mL | 732 ± 183 | 1459 ± 383 | 3445 ± 1328 |
| Cmax, 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 |
| tmax, days | 6.0 (3.0, 7.0) | 5.0 (5.0, 9.0) | 7.1 (3.0, 9.1) |
| t½, 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 |

Source: Panel 6. 2.7.2 Summary of Clinical Pharmacology Studies.
Abbreviations: $AUC_{0-\infty}$, area under the concentration–time curve from time 0 to infinity; $C_L$, clearance, $C_{L/F}$, clearance after oral administration; $C_{max}$, maximum concentration; $t_{1/2}$, terminal half-life; $T_{max}$, time to $C_{max}$, $V_d$, volume of distribution

## Safety Results

The single SC doses of 150 mg, 300 mg, and 600 mg tralokinumab in this trial were well tolerated. There were no safety concerns or ADAs identified in any subject.

***Reviewer's Comments***

(1) *After single SC dose administration at the dose range of 150 to 600 mg in Japanese subjects, tralokinumab systemic exposure increased in a dose-proportional manner, as assessed by $C_{max}$ and AUC and confirmed by statistical analysis.*
(2) *The mean $t_{½}$ was 20 to 25 days for the 150, 300, and 600 mg CAT-354 doses. The $C_{L/F}$ and volume of distribution parameters were similar within the investigated dose range.*

# 14.1.4. Study CAT-354-0602

## Title

A Double-Blind, Placebo-Controlled, Study to Assess the Pharmacokinetics, Safety, and Tolerability of Multiple Intravenous Doses at 3 Dose Levels of CAT-354 in Subjects With Moderate Asthma

## Objectives

The primary objective was to investigate the PK profile of multiple IV doses of CAT-354.

Secondary objectives were to determine the safety and tolerability of multiple IV doses of CAT-354.

## Trial Design

This was a randomized, double-blind, placebo-controlled trial in adults with moderate asthma, conducted at two sites in the United Kingdom.

A total of three dose levels of tralokinumab (1 mg/kg, 5 mg/kg, and 10 mg/kg) was studied in three sequential dose cohorts. Within each cohort, subjects were randomized in an 8:2 ratio to

tralokinumab or placebo, administered as a 30 min IV infusion on three occasions, 4 weeks apart. After their last dose, subjects were followed up for 13 weeks for assessment of PK, safety, pharmacodynamics (PD), and immunogenicity.

Blood samples for PK assessment were collected three times on each dosing day, at Weeks 0, 4, and 8 (predose, 10 min postdose, and 12 hr postdose), and additionally on Day 4 and at Weeks 1, 2, 3, 5, 9, 12, 15, and 21 (i.e., 13 weeks after the third dose).

**Subject Disposition and Baseline Demographics**

A total of 23 subjects was randomized, and all received at least one dose of CAT-354. Owing to slow recruitment, enrollment was closed before the planned number of 30 subjects was achieved. Sixteen subjects received all three doses of tralokinumab and completed the trial, and seven subjects were withdrawn from the trial after receiving one or two doses of CAT-354. The most common reason for withdrawal was an adverse event (AE) (five subjects: two receiving tralokinumab 1 mg/kg and one each receiving tralokinumab 5 mg/kg, 10 mg/kg, and placebo).

The demographic data were comparable across treatment groups. All subjects but one were men, and all but one were white. The mean age was 38.3 years (SD 9.8, range 21 to 60 years), the mean body weight was 81.4 kg (SD 14.6, range 56 to 114 kg), and the mean BMI was 25.3 $kg/m^2$ (SD 3.6, range 19 to 32 $kg/m^2$).

## Pharmacokinetic Results

Key PK parameters for tralokinumab are shown in Table 61. Systemic exposure to tralokinumab, as assessed by $C_{max}$ and AUC, appeared to increase in a dose-proportional manner across the dose range. Of note, only three subjects were randomized to the 10 mg/kg dose group, and only one subject in this group received all three doses of CAT-354. Nevertheless, the PK for the 10 mg/kg dose was broadly proportional to the PK for the lower doses (1 mg/kg and 5 mg/kg).

**Table 61. Pharmacokinetic Parameters for Tralokinumab After Single and Multiple Intravenous Doses (Trial CAT-354-0602)**

| 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) |
| $AUC_{\tau}$, 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 |

Source: Panel 8. 2.7.2 Summary of Clinical Pharmacology Studies.
[a] $AUC_{\tau}$, $AUC_{0-\infty}$, $C_{max}$, 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 ($AUC_{\tau}$ 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 AUC0-∞, for dose 3 based on $AUC_{0-28}$.
Abbreviations: AR, accumulation ratio after three doses, 4 weeks apart, calculated as $AUC_{Day\ 56-84}/AUC_{Day\ 0-28}$; AUC, area under the serum concentration–time curve; $AUC_{\tau}$, AUC over the dosing interval (Day 0 to 28 for dose 1, Day 56 to 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 distr bution (after IV dosing)

## Safety Results

Tralokinumab was well tolerated, with no evidence of a dose-relationship for AEs. No significant safety concerns were identified. There was no evidence of induction of immunogenicity by tralokinumab in any subject.

***Reviewer's Comments***

(1) *The PK of the 10 mg/kg dose appeared to be broadly proportional to the PK of the lower doses (1 mg/kg and 5 mg/kg) after multiple IV dose administration.*
(2) *$C_{max}$ and $C_{28}$ both increased by small amounts from the first dose through the third dose at all dose levels. These small increases were consistent with the calculated accumulation ratio, which is in the order of 1.4 to 1.7.*

## 14.1.5. Study MI-CP199

### Title

A Phase 2a, Randomized, Double-Blind, Placebo-Controlled, Parallel-Arm, Multicenter Study to Evaluate the Efficacy and Safety of CAT-354, a Recombinant Human Monoclonal Antibody Directed Against Interleukin-13 (Il-13), on Asthma Control in Adults With Uncontrolled, Moderate-to-Severe, Persistent Asthma

### Objectives

The primary objective was to evaluate the effect of three SC treatment regimens of CAT-354 versus placebo on asthma control at Study Day 92 in adults with uncontrolled, moderate-to-severe, persistent asthma.

A secondary objective was to investigate the PK and immunogenicity of tralokinumab. Several other secondary and exploratory objectives were investigated to assess safety, tolerability, efficacy, and asthma-related PD markers (not reported here).

### Trial Design

Subjects were randomized in a 1:1:1 ratio to three dose cohorts (tralokinumab 150 mg, 300 mg, or 600 mg SC). Within each cohort, subjects were randomized in a 3:1 ratio to tralokinumab or placebo. Subjects were dosed Q2W for 14 weeks (seven doses, with the last dose at Week 12), then followed up for 12 weeks after the last dose of tralokinumab for assessment of PK, safety, and immunogenicity.

Blood samples for PK assessment were collected predose at Weeks 0, 2, 4, 6, 8, 10, and 12 during the treatment period, and during Week 12 (3 days after the final dose) and at Weeks 13, 14, 18, and 24 in the follow-up period.

#### Subject Disposition and Baseline Demographics

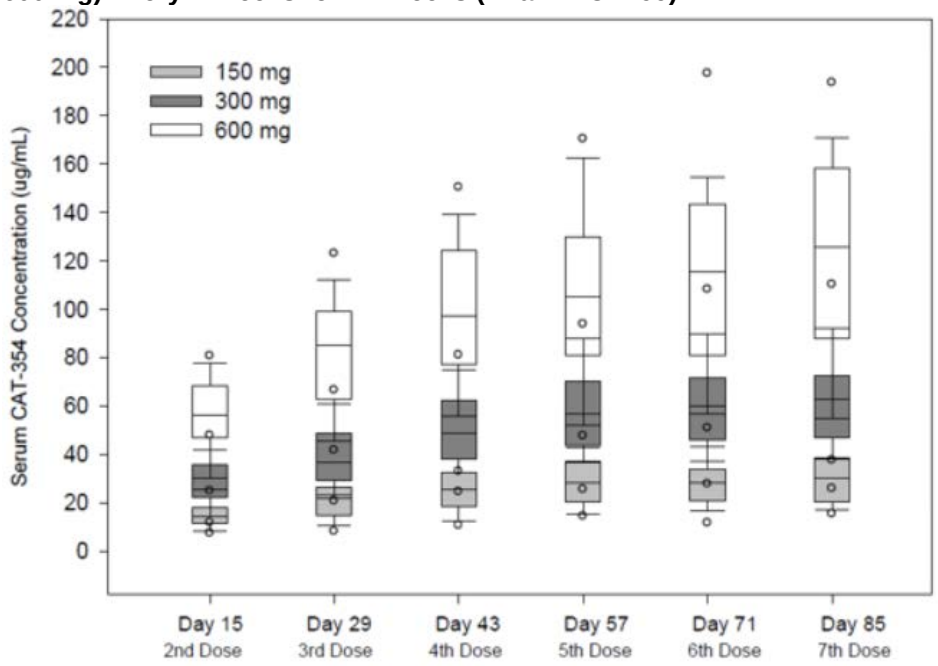
One hundred ninety-four subjects were randomized, and all received at least one dose of CAT-354. More than 91% of the subjects in each treatment group completed the trial, and more than 92% of the subjects in each treatment group received all seven doses of CAT-354. Four subjects receiving tralokinumab and four receiving placebo withdrew from the trial.

The demographic data were similar across treatment groups. Most subjects were white and not Hispanic or Latino, and 60% were female. The mean age was 47.3 years (SD 10.8, range 18 to 65 years), the mean body weight was 76.0 kg (SD 13.3, range 46 to 120 kg), and the mean BMI was 27.1 $kg/m^2$ (range 18.5 to 35.3 $kg/m^2$).

### Pharmacokinetic Results

Serum trough concentrations of tralokinumab increased in a dose-dependent manner (Figure 31). Within each dose group, the concentrations were comparable for the last two doses, indicating that steady state was reached.

**Figure 31.Trough Concentrations of Tralokinumab After Subcutaneous Dosing (150, 300, or 600 mg) Every 2 Weeks for 12 Weeks (Trial MI-CP199)**




Source: Panel 9, 2.7.2 Summary of Clinical Pharmacology Studies

## Safety Results

The safety profile of the tralokinumab doses administered in this trial was acceptable. There was no evidence of induction of immunogenicity by tralokinumab in any subject.

***Reviewer's Comments***

(1) *In the SC dose range of 150 to 600 mg, tralokinumab systemic exposure increased in a dose-proportional manner.*
(2) *Tralokinumab appeared to reach steady state around Day 71 to Day 85, following dosing once every 2 weeks.*

# 14.1.6. Study CD-RI-CAT-354-1049

## Title

A Phase 2b, Randomized, Double-Blind Study to Evaluate the Efficacy of Tralokinumab in Adults With Uncontrolled, Severe Asthma

## Objectives

The primary objective was to investigate the efficacy of two SC dosing regimens of tralokinumab in adults with uncontrolled, severe asthma requiring concomitant treatment with high-dose inhaled corticosteroids and long-acting β2-agonists.

A secondary objective was to investigate the PK and immunogenicity of tralokinumab. Several other secondary and exploratory objectives were included to assess safety, tolerability, efficacy, and asthma-related PD markers (not reported here).

## Trial Design

This was a randomized, double-blind, placebo-controlled trial, conducted at multiple sites in 15 countries (Argentina, Canada, Chile, the Czech Republic, France, Germany, Japan, Mexico, the Philippines, Poland, Russia, Spain, South Korea, the United Kingdom, and the United States).

Subjects were randomized in a 1:1 ratio to two cohorts: Q2W for 52 weeks (with last dose at Week 51), or Q2W for 12 weeks followed by every 4 weeks (Q4W) for 40 weeks (Q2/4W, with last dose at Week 49). Within each cohort, subjects were randomized in a 2:1 ratio to tralokinumab 300 mg SC or placebo. Subjects were followed up for 24 weeks after the last dose of CAT-354 for assessment of PK, safety, and immunogenicity.

Blood samples for PK assessment were collected predose at Weeks 1, 5, 13, 19, 25, 37, and 49 during the treatment period, and at Weeks 53, 59, 67, and 75 in the follow-up period.

**Subject Disposition and Baseline Demographics**

Four hundred fifty-two subjects were randomized, and all received at least one dose of CAT-354. More than 85% of the subjects in each treatment group completed the trial, and more than 72% of the subjects in each treatment group received all planned doses of CAT-354. The most frequent reason for not completing the trial or treatment was withdrawal of consent.

The demographic data were comparable across treatment groups. Most subjects were white and not Hispanic or Latino; and approximately two-thirds were female. The mean age was 50 years (range 18 to 75 years). For all subjects receiving tralokinumab, the mean body weight was 71.5 kg (SD 15.2, range 36 to 115 kg) and the mean BMI was 27.0 $kg/m^2$ (SD 4.7, range 16.0 to 39.9 $kg/m^2$). For all subjects receiving placebo, the mean body weight was 74.6 kg (SD 15.8, range 45 to 122 kg) and the mean BMI was 28.0 $kg/m^2$ (SD 5.2, range 18.9 to 40.0 $kg/m^2$).

## Pharmacokinetic Results

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 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 ratios of the mean trough concentration at Week 13 versus Week 5 ranged from 1.40 to 1.58.

## Safety Results

The safety profile of tralokinumab was acceptable for both dosing regimens. There were six subjects (2.0%) dosed with tralokinumab and seven subjects (4.6%) dosed with placebo who had confirmed postdose ADA-positive samples. Antibody titers ranged from 1 to 5 in the subjects with ADA-positive samples in the tralokinumab groups. The observed presence of ADAs did not influence the PK of tralokinumab, which could be attributable to the low antibody titers or to a transient response.

***Reviewer's Comments***

(1) *Following multiple-dose SC administration for 52 weeks, the exposure of tralokinumab in both tralokinumab-treated groups, based on observed minimum concentration ($C_{min}$), was in line with that seen in previous clinical studies. At Week 13, mean observed $C_{min}$ was similar between the 300 mg Q2W and Q2/4W groups (76.6 and 66.2 μg/mL, respectively).*
(2) *The mean exposure decreased by approximately a factor of 2 in the 300 mg Q2/4W group at Week 25 ($C_{min}$ 32.3 μg/mL), which confirmed linear PK of tralokinumab.*
(3) *Exposure levels 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, which indicated that steady-state levels were attained.*
(4) *Accumulation of tralokinumab by multiple dosing, as assessed by $C_{min}$, was seen, and the ratio of trough concentrations of Week 13 versus Week 5 ranged from 1.40 to 1.58.*

## 14.1.7. Study D2213C00001

### Title

A Phase 2b, Randomized, Double-Blinded, Placebo-Controlled, Dose-Ranging Study to Evaluate the Efficacy and Safety of Tralokinumab in Adult Subjects With Moderate-to-Severe Atopic Dermatitis

### Objectives

The primary objective was to evaluate the efficacy of tralokinumab in adults with moderate-to-severe AD.

A secondary objective was to characterize the PK and immunogenicity of tralokinumab, and an exploratory objective was to explore the effect of different doses of tralokinumab on blood biomarkers that might predict or reflect efficacy response. Further secondary and exploratory objectives were included to assess safety, tolerability, efficacy, and response characteristics.

### Trial Design

Subjects were randomized in a 1:1:1:1 ratio to tralokinumab 45 mg, 150 mg, or 300 mg, or placebo Q2W for 12 weeks (six doses, with the last dose at Week 10), administered SC with concomitant use of TCS. The randomization was stratified to ensure that each dose cohort included approximately 6 Japanese subjects (in Japan) and 40 non-Japanese subjects (in other countries). Subjects were followed up for 12 weeks after the last dose of CAT-354 for assessment of PK, safety, maintenance of effect, PD, and immunogenicity.

Blood samples for assessment of tralokinumab serum concentrations were collected predose at Weeks 0, 2, and 4, and at Weeks 12 and 22 during the follow-up. Blood samples for assessment of the serum biomarkers periostin, dipeptidyl peptidase 4 (DPP-4), and C-C motif chemokine ligand 17 (CCL17) were collected at Weeks 0, 4, 12, and 22, and blood samples for assessment of IgE were collected at Weeks 0 and 12.

**Subject Disposition and Baseline Demographics**

Two hundred four subjects were randomized, and all received at least one dose of tralokinumab. More than 76% of the subjects in each treatment group completed the trial, and more than 60% of the subjects in each treatment group received all planned doses of CAT-354. The most frequent reason for not completing the trial or treatment was withdrawal of consent.

The demographic data were generally similar across treatment groups. Sixty-one percent of the subjects were white, 22% were Asian, and 14% were black/African-American. Most of the subjects were not Hispanic or Latino, and almost half were female. The mean age was 37.8 years (SD 14.5, range 18 to 74 years), the mean body weight was 77.5 kg (SD 19.0, range 42 to 129 kg), and the mean BMI was 27.0 kg/m$^2$ (range 15.1 to 47.5 kg/m$^2$).

## Pharmacokinetic Results

Serum trough concentrations of tralokinumab are presented in Table 62. The concentrations increased in a dose-dependent manner.

**Table 62. Trough Concentrations of Tralokinumab After Subcutaneous Dosing (45, 150, or 300 mg) Every 2 Weeks for 10 Weeks (Trial D2213C00001).**

| Week | Tralokinumab dose group | | |
|---|---|---|---|
| | 45 mg (N=50) | 150 mg (N=51) | 300 mg (N=52) |
| $C_{trough}$ Week 2, µg/mL | 4.35 ± 2.01 | 16.2 ± 6.1 | 28.9 ± 12.6 |
| $C_{trough}$ Week 4, µg/mL | 7.94 ± 3.36 | 26.5 ± 10.5 | 44.3 ± 23.3 |
| $C_{trough}$ Week 12, µg/mL | 13.1 ± 8.0 | 37.7 ± 21.8 | 61.5 ± 45.0 |
| $C_s$ Week 22, µg/mL | 1.18 ± 1.11 | 3.63 ± 4.54 | 5.69 ± 6.05 |

**Note:** Values are given as geometric mean ± standard deviation.

**Abbreviations:** $C_s$ = serum concentration; $C_{trough}$ = serum trough concentration; N = number of subjects in analysis set.

Source: Panel 10. 2.7.2 Summary of Clinical Pharmacology Studies.

## Pharmacodynamic Results

**Serum Biomarkers: Periostin, CCL17, IgE, and DPP-4**

For the serum levels of periostin and CCL17, a significant reduction from baseline to Week 12 was observed in all three tralokinumab dose groups compared with placebo ($p<0.001$), with the largest reduction in the tralokinumab 300 mg group (32% reduction for periostin, 49% for CCL17). Similarly, serum IgE was significantly reduced from baseline to Week 12 in the tralokinumab 150 and 300 mg groups compared with placebo ($p<0.001$), and the largest reduction (24%) was observed with tralokinumab 300 mg. For DPP-4, an increased serum level was observed in all three tralokinumab groups compared with placebo, most notably with tralokinumab 150 and 300 mg, although not statistically significant.

**Skin Biomarker: *S. aureus* Colonization**

Compared with subjects in the placebo group, a significantly lower percentage of subjects in all three tralokinumab dose groups was positive for *S. aureus* at Week 12 ($p<0.05$). Of the subjects

in the tralokinumab 300 mg group, 35% were positive in lesional skin and 8% in nonlesional skin; in the placebo group, 73% in lesional and 40% in nonlesional skin.

Furthermore, the percentage of subjects shifting from being positive for *S. aureus* at baseline to being negative at Week 12 was higher in the three tralokinumab groups than in the placebo group, both for lesional and nonlesional skin.

## Safety Results

The safety profile of tralokinumab was reasonable in the three treatment groups, and no dose-related safety events were identified. One subject (2.0%) in the tralokinumab 300 mg group had a confirmed ADA-positive sample postdose. Antibody titers were low and there was no indication of any impact of ADA on the observed PK of tralokinumab in the subject.

***Reviewer's Comments***

(1) *Blood samples were collected predose and at trough tralokinumab levels. The trough concentrations of tralokinumab increased in a dose-dependent manner.*
(2) *Compared with placebo, tralokinumab had a normalizing effect on key serum biomarkers of AD. Furthermore, a broad anti-inflammatory effect was observed in subjects receiving tralokinumab, demonstrated by reduction of inflammatory skin biomarkers. Skin colonization with* S. aureus *was strongly suppressed in subjects receiving tralokinumab compared with subjects receiving placebo. These findings confirm the mode of action of tralokinumab and support its clinical efficacy in improving disease symptoms in patients with AD.*

# 14.1.8. Study ECZTRA-1 (LP0162-1325)

## Title

Tralokinumab Monotherapy for Moderate-to-Severe Atopic Dermatitis, ECZTRA-1

## Objectives

The primary objective was to evaluate the efficacy of tralokinumab in adults with moderate-to-severe AD during an initial 16-week treatment period. Secondary, other, and maintenance objectives included evaluation of safety, tolerability, and a range of efficacy outcomes. One of the 'other' objectives was to evaluate the incidence of skin colonization with *S. aureus* at Week 16. Furthermore, serum and skin biomarkers were evaluated as an exploratory part of the trial to profile the molecular response to tralokinumab treatment.

## Trial Design

For the initial treatment period (Weeks 0 to 16), subjects were randomized in a 3:1 ratio to tralokinumab 300 mg or placebo Q2W (administered SC), following an initial loading dose (tralokinumab 600 mg or placebo). For the subsequent maintenance treatment period (Weeks 16 to 52), a subject's treatment depended on their initial treatment regimen and clinical response (defined as an IGA score of 0 or 1 or Eczema Area and Severity Index [EASI]-75) at Week 16. Subjects randomized to tralokinumab in the initial treatment period who had a clinical response at Week 16 were rerandomized in a 2:2:1 ratio to a maintenance regimen of tralokinumab

300 mg Q2W, tralokinumab 300 mg Q4W, or placebo Q2W. This randomization was stratified by region and IGA response at Week 16 (IGA 0/1 or IGA >1). Subjects randomized to placebo in the initial treatment period who had a clinical response at Week 16 continued to receive placebo Q2W.

Subjects without a clinical response at Week 16, as well as those who met prespecified criteria indicating insufficient response during maintenance treatment, were transferred to open-label treatment with tralokinumab 300 mg Q2W and optional use of TCS up to Week 52.

Subjects were followed up for 16 weeks after the last dose of tralokinumab for assessment of safety, PK, and immunogenicity. In some countries, subjects had the option to transfer to ECZTEND (pivotal Phase 3 study) between the end-of-treatment and safety follow-up visits; these subjects did not attend the final safety follow-up visit during ECZTRA-1.

Blood samples for assessment of tralokinumab serum concentrations were collected predose at Weeks 2, 4, 14, 16, 28, and 52, during the mid-dosing interval at Week 15, and at the safety follow-up. AUC was calculated based on the serum concentrations measured at Weeks 14, 15, and 16. Blood samples for assessment of serum biomarkers (including but not limited to: periostin, DPP-4, human beta-defensin 2, CCL17, IL-13, IL-17, IL-22, and beta-defensin 4A were collected at Weeks 0, 4, 8, 16, 28, and 52. Furthermore, blood samples for two serum biomarkers (IgE and lactate dehydrogenase [LDH]) that were part of the clinical laboratory tests were collected every 4 weeks from Weeks 0 to 52, and at the safety follow-up.

At selected trial sites, the following optional samples (requiring additional informed consent) were taken: blood samples for assessment of additional serum biomarkers at Weeks 0, 4, 8, 16, 28, and 52, biopsies for assessment of skin biomarkers at Weeks 0, 4, and 16, skin swabs for assessment of *S. aureus* colonization at Weeks 0, 16, and 52, and (data not included in this application) skin swabs for characterization of the skin microbiome at Weeks 0, 8, 16, and 52.

**Subject Disposition and Baseline Demographics**

In the initial treatment period, 802 subjects were randomized to treatment and 602 of these received at least one dose of tralokinumab. In the maintenance period, 214 responders were assigned to treatment and 144 of these received at least one dose of tralokinumab. Furthermore, 506 nonresponders were transferred to (and received at least one dose) open-label tralokinumab treatment at Week 16 after initial treatment with tralokinumab (361 subjects) or placebo (145 subjects). More than 79% of subjects in each tralokinumab group (in any period) received all planned doses of tralokinumab.

The demographic data were generally similar across treatment groups. Seventy percent of the subjects were white, 20% were Asian, and 7% were black/African-American. Most of the subjects were not Hispanic or Latino, and almost half were female. The mean age was 38.8 years (SD 14.1, range 18 to 92 years), the mean body weight was 76.0 kg (SD 18.9, range 37 to 165 kg), and the mean BMI was 26.0 $kg/m^2$ (SD 5.8, range 15.5 to 61.3 $kg/m^2$) (M5.3.5.1 ECZTRA-1 CTR Section 7.4 and Table 1.15).

## Pharmacokinetic Results

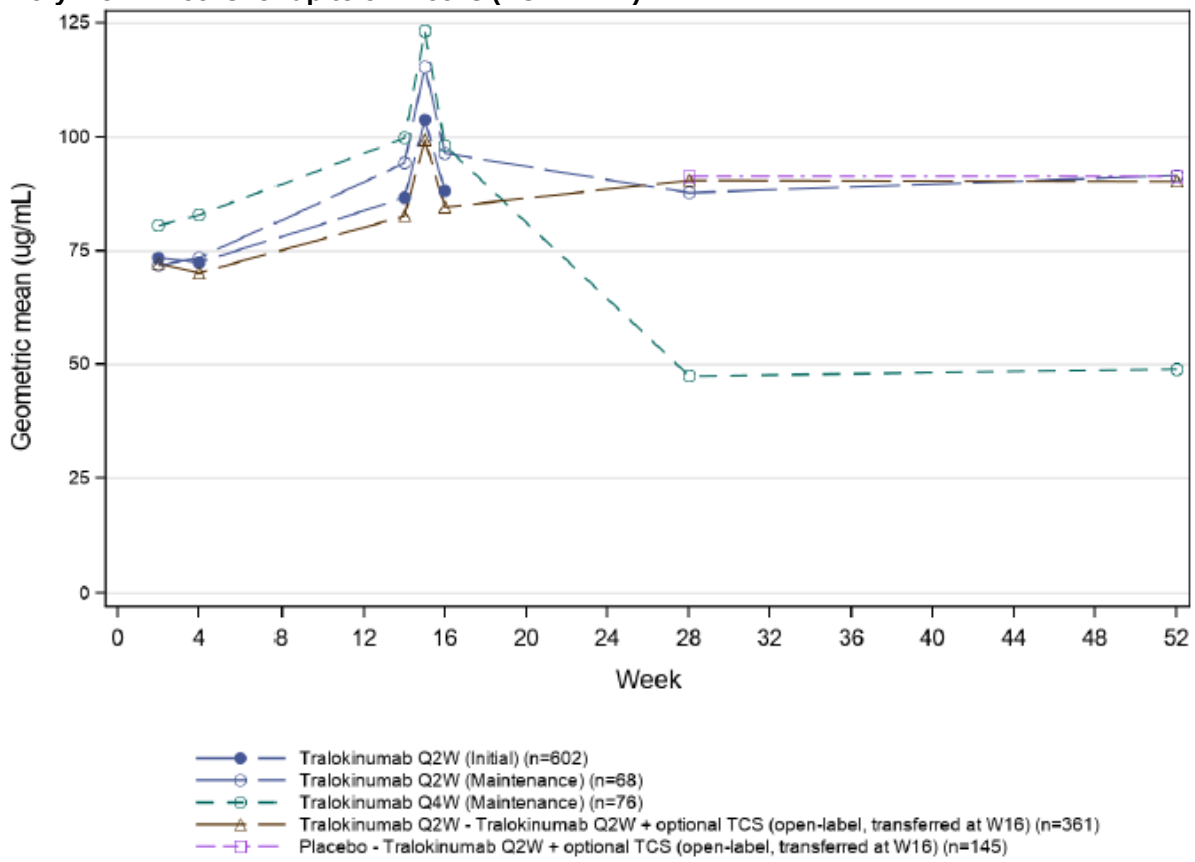
The mean trough concentrations of tralokinumab over time, together with the mean serum concentration at Week 15, sampled between two trough concentrations are shown in Figure 32.

This sampling time point in the middle of a dosing interval approximates the time to maximum concentration observed for tralokinumab in previous trials, and the observed peak at Week 15, therefore, represents the expected $C_{max}$.

Subjects receiving tralokinumab in the initial treatment period had reached steady state by Week 16; the geometric mean trough concentration was 88.3 µg/mL (SD 43.6; n=602). Subjects receiving placebo in the initial treatment period and transferred at Week 16 to open-label tralokinumab treatment had reached steady state by the next sampling time point at Week 28.

After the switch at Week 16 from Q2W to Q4W in the Q2/4W group, the mean trough concentration at Week 28 in this group was approximately half that at Week 16, consistent with linear PK.

**Figure 32. Mean Serum Concentrations of Tralokinumab After Subcutaneous Dosing (300 mg) Every 2 or 4 Weeks for up to 52 Weeks (ECZTRA-1)**




Q2W: Every 2 weeks, Q4W: Every 4 weeks
Data collected after permanent discontinuation of IMP not included
21FEB2020-WABANSCE\T_TRALO_TROUGH.sas\t_900397_tralo_trough_e1

Source: Panel 11. 2.7.2 Summary of Clinical Pharmacology Studies.
Trough concentrations, plus a mid-dosing interval concentration at Week 15, shown as geometric means for the following subjects:

- 602 subjects receiving tralokinumab 300 mg Q2W from Weeks 0-16 (following a 600 mg loading dose).
- 68 subjects receiving tralokinumab 300 mg Q2W from Weeks 0-52 or until treatment discontinuation / transfer to open-label tralokinumab.
- 76 subjects receiving tralokinumab 300 mg Q2W from Weeks 0-16 and Q4W from Weeks 16-52 or until treatment discontinuation/transfer to open-label tralokinumab.
- 361 subjects receiving tralokinumab 300 mg Q2W from Weeks 0-16 and transferred at Week 16 (due to lack of clinical response) to open-label tralokinumab 300 mg Q2W and optional TCS.
- 145 subjects receiving placebo from Weeks 0-16 and open-label tralokinumab 300 mg Q2W (without loading dose) and optional TCS from Weeks 16-52 or until treatment discontinuation (excluding subjects transferred to open-label arm after Week 16).

Abbreviations: ECZTRA, ECZema TRAlokinumab; n, number of subjects in each treatment group at Week 16, except for the total number given for the initial treatment period (602), which corresponds to the number of subjects at Week 0; TCS, topical corticosteroids; Q2W, every 2 weeks; Q4W, every 4 weeks

# Pharmacodynamic Results

## Serum Biomarkers: Change From Baseline in Median Serum Concentration

During the initial treatment period, the levels of the Th2-related biomarkers, CCL17 and periostin, were reduced at Week 4 in the tralokinumab group (56% and 20% reduction, respectively), with further reductions at Week 16 (70% and 33% reduction, respectively). The levels were only marginally changed in the placebo group at Week 16 (6% and 7% reduction, respectively). The level of the Th22 cytokine IL-22 was reduced by 57% in the tralokinumab

group and by 38% in the placebo group at Week 16. The level of hBD2 was reduced by 27% in the tralokinumab group and by 15% in the placebo group at Week 16. The level of DPP-4 was only minimally affected in the tralokinumab group, with an increase of 7% at Week 16. The serum markers remained stable during the maintenance and open-label treatment periods, except for a further reduction of CCL17 in subjects receiving tralokinumab.

**Skin Biomarkers: Change From Baseline to Week 16 in Biopsies From Lesional Skin**

Epidermal thickness and the expression levels of keratin 16 and the hyperproliferation marker Ki-67 decreased in the tralokinumab group and remained largely unchanged in the placebo group. The expression level of the antimicrobial protein S100A7 decreased in the tralokinumab group and remained elevated in the placebo group. The expression levels of the barrier proteins loricrin and filaggrin increased in the tralokinumab group and remained low in the placebo group. Furthermore, the numbers of CD11c-positive dendritic cells and macrophages decreased in the tralokinumab group and increased slightly in the placebo group.

Reduced mRNA expression of the general inflammatory marker MMP12, and of genes related to type 2 inflammation (CCL2, CCL11, CCL13, CCL17, CCL18, and CCL26) was observed in the tralokinumab group. Similarly, reduced mRNA expression of Th17- and Th22-regulated genes (CXCL1, PI3, S100A7, S100A9, and S100A12) was observed in the tralokinumab group. In addition, increased mRNA expression of the lipid metabolism marker ELOVL3 and the barrier tight junction marker CLDN23 was observed in the tralokinumab group. Together with increased loricrin expression, this indicated an improved barrier function in subjects treated with tralokinumab.

**Skin Colonization by *S. aureus***

During the initial treatment period, skin colonization with *S. aureus* was reduced from 969 to 22 gene copies/$cm^2$ (median values) in the tralokinumab group and from 649 to 238 gene copies/$cm^2$ in the placebo group. This corresponds to a 10-fold reduction in the tralokinumab group relative to the placebo group (ratio of 0.09 [$p<0.0001$]) for tralokinumab versus placebo in change from baseline to Week 16. After rerandomization at Week 16, *S. aureus* colonization was low in all groups during the maintenance treatment period. For subjects transferring to open-label treatment with tralokinumab, the *S. aureus* colonization was further reduced from 56 to 14 gene copies/$cm^2$ (median values) between Week 16 and Week 52.

## Immunogenicity (Safety) Results

Tralokinumab was well-tolerated with an acceptable safety profile for both dosing regimens. During the initial treatment period, 10 (1.7%) of the subjects treated with tralokinumab and 1 (0.5%) of those treated with placebo had treatment-emergent ADA. During the entire trial, 28 (3.7%) tralokinumab-treated subjects had a treatment-emergent ADA response, which was persistent for 8 (1.1%) subjects, indeterminate for 9 (1.2%) subjects, and transient for 11 (1.5%) subjects. One (0.5%) of the tralokinumab-naïve subjects had a treatment-emergent ADA response, which was transient. Three tralokinumab-treated subjects tested positive for nAb.

***Reviewer's Comments***

(1) *The IGA 0/1 and EASI-75 response rates at Week 16 were statistically significantly higher with tralokinumab Q2W than with placebo, demonstrating that tralokinumab Q2W was superior to placebo in treating moderate-to-severe AD.*
(2) *With dosing regimen switch at Week 16 from Q2W to Q4W in the Q2/4W group, the mean trough concentration of tralokinumab at Week 28 in this group was approximately half that at Week 16, which indicated linear PK within the investigated dose range.*

### 14.1.9. Study ECZTRA-2 (LP0162-1326)

## Title

Tralokinumab Monotherapy for Moderate-to-Severe Atopic Dermatitis, ECZTRA-2

## Objectives and Trial Design

The design and objectives of this trial were the same as those of ECZTRA-1, except that there was no evaluation of skin colonization by *S. aureus* and no exploratory evaluation of skin and serum biomarkers other than the two serum biomarkers (IgE and LDH) that were part of the clinical laboratory tests.

**Subject Disposition and Baseline Demographics**

In the initial treatment period, 794 subjects were randomized to treatment and 592 of these received at least one dose of tralokinumab. In the maintenance period, 258 responders were assigned to treatment and 180 of these received at least one dose of tralokinumab. Furthermore, 469 nonresponders were transferred to (and received at least one dose) open-label tralokinumab treatment at Week 16 after initial treatment with tralokinumab (324 subjects) or placebo (145 subjects). More than 76% of the subjects in each tralokinumab group (in any period) received all planned doses of tralokinumab.

The demographic data were generally similar across treatment groups. Sixty-three percent of the subjects were white, 26% were Asian, and 8% were black/African American. Most of the subjects were not Hispanic or Latino, and almost half were female. The mean age was 36.7 years (SD 14.6, range 18 to 86 years), the mean body weight was 76.1 kg (SD 17.9, range 42 to 156 kg), and the mean BMI was 26.3 $kg/m^2$ (SD 5.7, range 16.5 to 57.5 $kg/m^2$).

## Pharmacokinetic Results

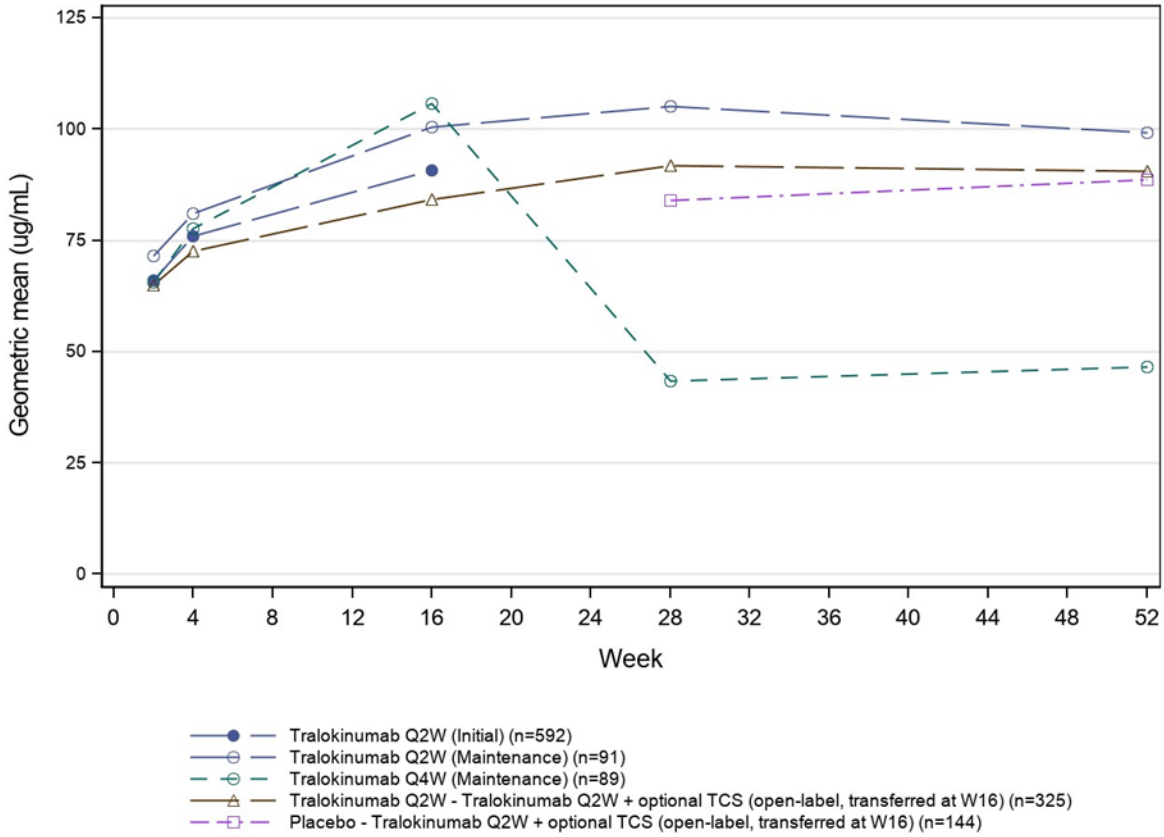
The mean trough concentrations of tralokinumab over time are shown in Figure 33. Subjects receiving tralokinumab in the initial treatment period had reached steady state by Week 16; the geometric mean trough concentration was 90.7 µg/mL (SD 42.7; n=592). Subjects receiving placebo in the initial treatment period and transferred at Week 16 (due to lack of clinical response) to open-label tralokinumab treatment had reached steady state by the next sampling time point at Week 28.

Across all sampling time points, the mean trough concentrations for the two groups of nonresponders (placebo or tralokinumab) transferred at Week 16 to open-label tralokinumab

Q2W were slightly lower than the trough concentrations for tralokinumab responders receiving tralokinumab Q2W.

After the switch at Week 16 from Q2W to Q4W in the Q2/4W group, the mean trough concentration at Week 28 was approximately half that at Week 16, consistent with linear PK.

**Figure 33. Mean Serum Concentrations of Tralokinumab After Subcutaneous Dosing (300 mg) Every 2 or 4 Weeks for up to 52 Weeks (ECZTRA-2)**




Q2W: Every 2 weeks, Q4W: Every 4 weeks
Data collected after permanent discontinuation of IMP not included
21FEB2020-WABANSCE\T_TRALO_TROUGH.sas\t_900399_tralo_trough_e2

Source: M2.7.2 Appendix 1 Figure 2.
Trough concentrations shown as geometric mean for the following groups of subjects:

- 592 subjects receiving tralokinumab 300 mg Q2W from Weeks 0-16 (following a 600 mg loading dose).
- 91 subjects receiving tralokinumab 300 mg Q2W from Weeks 0-52 or until treatment discontinuation / transfer to open-label tralokinumab.
- 89 subjects receiving tralokinumab 300 mg Q2W from Weeks 0-16 and Q4W from Week 16-52 or until treatment discontinuation / transfer to open-label tralokinumab.
- 325 subjects receiving tralokinumab 300 mg Q2W from Weeks 0-16 and transferred at Week 16 (due to lack of clinical response) to open-label tralokinumab 300 mg Q2W and optional TCS.
- 144 subjects receiving placebo from Weeks 0-16 and open-label tralokinumab 300 mg Q2W (without loading dose) and optional TCS from Weeks 16-52 or until treatment discontinuation (excluding subjects transferred to open-label arm after Week 16).

Abbreviations: ECZTRA, ECZema TRAlokinumab; n, number of subjects in each treatment group at Week 16, except for the total number given for the initial treatment period (592), which corresponds to the number of subjects at Week 0; TCS, topical corticosteroids

## Immunogenicity (Safety) Results

Tralokinumab was well tolerated with an acceptable safety profile for both dosing regimens.

During the initial treatment period, eight (1.4%) of the subjects treated with tralokinumab and two (1.0%) of those treated with placebo had treatment-emergent ADA. During the entire trial, 47 (6.3%) tralokinumab-treated subjects had a treatment-emergent ADA response, which was persistent for 6 (0.8%) subjects, indeterminate for 20 (2.7%) subjects, and transient for 21 (2.8%) subjects. Two (0.3%) tralokinumab-treated subjects had treatment-boosted ADA. Two (1.0%) tralokinumab-naïve subjects had a treatment-emergent ADA response, which was indeterminate. Eight tralokinumab-treated subjects tested positive for nAb.

***Reviewer's Comments***

(1) *The IGA 0/1 and EASI-75 response rates at Week 16 were statistically significantly higher with tralokinumab Q2W than with placebo, demonstrating that tralokinumab Q2W was superior to placebo in treating moderate-to-severe AD.*
(2) *With dosing regimen switch at Week 16 from Q2W to Q4W in the Q2/4W group, the mean trough concentration of tralokinumab at Week 28 was approximately half that at Week 16, which indicated linear PK within the investigated dose range.*

## 14.1.10. Study ECZTRA-3 (LP0162-1339)

### Title

Tralokinumab in Combination With Topical Corticosteroids for Moderate-to-Severe Atopic Dermatitis, ECZTRA-3

### Objectives

The primary objective was to demonstrate superior efficacy of tralokinumab versus placebo when both were used in combination with TCS. Secondary, maintenance, and other objectives included evaluation of safety and a range of efficacy outcomes.

### Trial Design

This was a randomized, double-blind, placebo-controlled trial in subjects with moderate-to-severe AD conducted in multiple countries.

For the initial treatment period (Weeks 0 to 16), subjects were randomized in a 2:1 ratio to tralokinumab 300 mg+TCS or placebo+TCS Q2W (administered SC), following an initial loading dose (tralokinumab 600 mg or placebo). For the subsequent continuation treatment period (Weeks 16 to 32), a subject's treatment depended on their initial treatment regimen and clinical response (defined as IGA of 0 or 1, or EASI-75) at Week 16. Subjects randomized to tralokinumab in the initial treatment period who had a clinical response at Week 16 were rerandomized in a 1:1 ratio to a continuation regimen of tralokinumab 300 mg Q2W or Q4W+TCS. This randomization was stratified by region and IGA response (IGA 0/1 or IGA >1).

Subjects randomized to placebo in the initial treatment period who had a clinical response at Week 16 continued to receive placebo+TCS Q2W. All subjects without a clinical response at Week 16 were assigned in a blinded manner to tralokinumab+TCS Q2W in the continuation treatment period.

Subjects were followed up for 16 weeks after the last dose of tralokinumab for assessment of safety, PK, and immunogenicity.

Blood samples for assessment of tralokinumab serum concentrations were collected predose at Weeks 4, 16, and 32, and at the safety follow-up. Blood samples for two serum biomarkers (IgE and LDH) that were part of the clinical laboratory tests were collected every 4 weeks from Weeks 0 to 32, and at the safety follow-up.

**Subject Disposition and Baseline Demographics**

In the initial treatment period, 380 subjects were randomized to treatment and 252 of these subjects received at least one dose of tralokinumab. In the continuation treatment period, 138 subjects were randomized as responders (69 from each tralokinumab group in the initial period) and received at least one dose of tralokinumab. Furthermore, 174 subjects were assigned as nonresponders and received at least one dose of tralokinumab in the continuation treatment period, after initial treatment with tralokinumab (95 subjects) or placebo (79 subjects). More than 83% of subjects in each tralokinumab group (in any period) received all planned doses of tralokinumab. The demographic data were overall well-balanced across treatment groups. Seventy-six percent of the subjects were white, 11% were Asian, and 9% were black/African American. Most were not Hispanic or Latino, and almost half were female. The mean age was 39.1 years (SD 15.2, range 18 to 80 years), the mean body weight was 79.4 kg (SD 18.7, range 46 to 148 kg), and the mean BMI was 27.4 kg/$m^2$ (SD 6.3, range 15.7 to 60.0 kg/$m^2$).

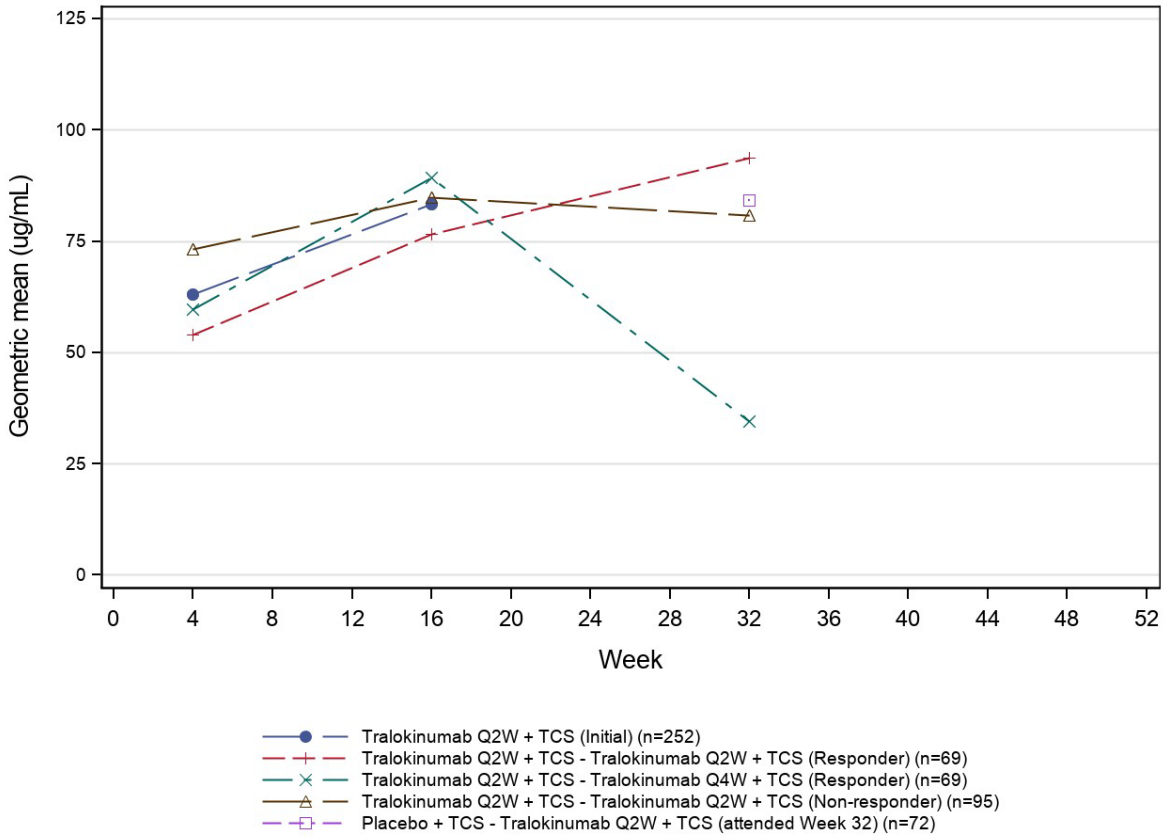
## Pharmacokinetic Results

The mean trough concentrations of tralokinumab over time are shown in Figure 34. Subjects receiving tralokinumab in the initial treatment period had reached steady state by Week 16; the geometric mean trough concentration was 83.3 µg/mL (SD 41.1; n=252).

For the tralokinumab responders receiving tralokinumab Q2W in both treatment periods, the geometric mean trough concentration at Week 16 was slightly lower than that observed in the other treatment groups. The arithmetic mean and median values, however, were similar across the groups. After the switch at Week 16 from Q2W to Q4W in the Q2/4W group, the mean trough concentration at Week 28 in this group was approximately half that at Week 16, consistent with linear PK.

For subjects receiving placebo in the initial treatment period and assigned to tralokinumab Q2W at Week 16 (due to lack of clinical response), the mean trough concentration at the next sampling time point at Week 32 was similar to the steady-state levels observed for the other groups receiving tralokinumab Q2W.

**Figure 34. Mean Serum Concentrations of Tralokinumab After Subcutaneous Dosing (300 mg) Every 2 or 4 Weeks for up to 32 Weeks**




Q2W: Every 2 weeks, Q4W: Every 4 weeks
Data collected after permanent discontinuation of IMP not included
21FEB2020-WABANSCE\T_TRALO_TROUGH.sas\t_900401_tralo_trough_e3

Source: M2.7.2 Appendix 1 Figure 3.
Trough concentrations shown as geometric mean for the following groups of subjects:

- 252 subjects receiving tralokinumab 300 mg Q2W+TCS from Weeks 0-16 (following a 600 mg loading dose).
- 69 subjects receiving tralokinumab 300 mg Q2W+TCS from Weeks 0-32 or until treatment discontinuation.
- 69 subjects receiving tralokinumab 300 mg Q2W+TCS from Weeks 0-16 and Q4W+TCS from Weeks 16-32 or until treatment discontinuation.
- 95 subjects receiving tralokinumab 300 mg Q2W+TCS from Weeks 0-16 and re-assigned at Week 16 (due to lack of clinical response) to tralokinumab 300 mg Q2W+TCS.

Does not include subjects receiving placebo+TCS from Weeks 0-16 and tralokinumab 300 mg Q2W+TCS from Weeks 16-32.
Abbreviations: n, number of subjects in each treatment group at Week 16, except for the total number given for the initial treatment period (252), which corresponds to the number of subjects at Week 0; TCS, topical corticosteroids

## Immunogenicity (Safety) Results

Tralokinumab used in combination with TCS was well-tolerated and had an acceptable safety profile for both dosing regimens. During the initial treatment period, one (0.4%) of the subjects treated with tralokinumab and two (1.6%) of those treated with placebo had treatment-emergent ADA. During the trial, seven (2.1%) tralokinumab-treated subjects had a treatment-emergent ADA response, which was indeterminate for six (1.8%) and transient for one (0.3%) subject. Three (2.4%) tralokinumab-naïve subjects had a treatment-emergent ADA response, which was indeterminate for two (1.6%) subjects and transient for one (0.8%) subject. Of the 10 subjects with treatment-emergent ADA, 8 tested positive for nAb; 1 of these subjects was tralokinumab-naïve.

***Reviewer's Comments***

(1) *The IGA 0/1 and EASI-75 response rates at Week 16 were statistically significantly higher with tralokinumab Q2W+TCS than with placebo+TCS, demonstrating that tralokinumab Q2W+TCS was superior to placebo+TCS in treating moderate-to-severe AD.*
(2) *With the dosing regimen switch at Week 16 from Q2W to Q4W in the Q2/4W group, the mean trough concentration of tralokinumab at Week 28 was approximately half that at Week 16, which indicated linear PK within the investigated dose range.*
(3) *For the tralokinumab responders receiving tralokinumab Q2W in both treatment periods, the geometric mean trough concentration at Week 16 was slightly lower than that in the other treatment groups. Per the Applicant, the lower geometric mean in the Q2W/Q2W group appears to be driven by a few low concentrations measured in this group.*

## 14.1.11. Study ECZTRA-5 (LP0162-1341)

### Title

Vaccine Responses in Tralokinumab-Treated Atopic Dermatitis

### Objectives

The primary objective of this trial was to demonstrate noninferiority of tralokinumab versus placebo with respect to immune responses to concomitantly administered vaccines. The trial assessed immunization responses against two nonlive vaccines, a combined Tdap vaccine and a meningococcal vaccine. Secondary and other objectives included evaluation of efficacy, safety, and tolerability of tralokinumab administered concomitantly with vaccines.

### Trial Design

This was a randomized, double-blind, placebo-controlled trial in subjects with moderate-to-severe AD conducted at multiple sites in Canada and the United States.

Subjects were randomized 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 one dose of each vaccine before the administration of tralokinumab or placebo.

Subjects were followed up for 16 weeks after the last dose of tralokinumab for assessment of safety, PK, and immunogenicity. Blood samples for assessment of tralokinumab serum concentrations were collected predose at Weeks 4 and 16, and at the safety follow-up. Blood samples for two serum biomarkers (IgE and LDH) that were part of the clinical laboratory tests were collected every 4 weeks from Weeks 0 to 16, and at the safety follow-up.

#### Subject Disposition and Baseline Demographics

Two hundred fifteen subjects were randomized to treatment, and one hundred six of these received at least one dose of tralokinumab. Most subjects received all planned doses of tralokinumab. More than 81% of the subjects in each treatment group completed the treatment period.

The demographic data were generally similar across treatment groups, except for the sex distribution: there was an equal distribution of men and women in the tralokinumab group and a majority of women in the placebo group. Fifty-five percent of the subjects were white, 16% were Asian, and 24% were black/African American. Most were not Hispanic or Latino. The mean age was 34.2 years (SD 11.0, range 18 to 54 years), the mean body weight was 80.8 kg (SD 22.1, range 44 to 162 kg), and the mean BMI was 28.6 kg/m$^2$ (SD 7.2, range 17.2 to 53.5 kg/m$^2$).

## Pharmacokinetic Results

The geometric mean trough concentration of tralokinumab was 65.4 µg/mL at Week 4 (SD 29.6, n=103) and 80.5 µg/mL at Week 16 (SD 41.4 µg/mL, n=95). At Week 30, the geometric mean serum concentration had decreased to 4.58 µg/mL (SD 43.7 µg/mL, n=8).

## Pharmacodynamic Results

### Vaccine Response

The percentage of subjects achieving each of the primary endpoints, positive antitetanus response and positive antimeningococcal response at Week 16, was similar in the tralokinumab group and the placebo group (Table 63). For the estimated difference in response rate, the lower limit of the 95% CI was greater than the prespecified noninferiority margin of -25%, demonstrating noninferiority of tralokinumab versus placebo with respect to immune responses to concomitantly administered, nonlive vaccines.

**Table 63. Positive Vaccine Response at Week 16 (Per Protocol Analysis Set), ECZTRA-5**

| | Tralokinumab Q2W (n= 88) | Placebo (n= 78) | |
|---|---|---|---|
| Vaccine response at Week 16 | Responders (%)[1] | 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) |

02DEC19:13:10:50 LP0162-1341 t 200001 vacc wk16 pp.doc

Source: M5.3.5.1 ECZTRA-5 CTR Panel 23.
Responders/total.
Mantel–Haenszel risk difference, stratified by baseline IGA.
Abbreviations: CI, confidence interval; ECZTRA, ECZema TRAlokinumab; IGA, Investigator's Global Assessment; Q2W, every 2 weeks

### Serum Biomarkers (IgE and LDH)

For IgE, the median levels were above the upper limit of the normal reference range at baseline for both tralokinumab (779 international units [IU]/mL) and placebo (387 IU/mL) (reference range 0 to 158 IU/mL). During the treatment period, the median level decreased by approximately 30% in the tralokinumab group (to 541 IU/mL at Week 16) but remained largely unchanged in the placebo group.

For LDH, the mean levels were within the normal reference range from baseline throughout treatment in both treatment groups.

## Safety Results

Tralokinumab used in combination with vaccines was well tolerated and had an acceptable safety profile.

During the entire trial, two (1.9%) subjects treated with tralokinumab had a treatment-emergent ADA response, which was indeterminate. Three (2.8%) subjects treated with placebo had a treatment-emergent ADA response, which was persistent, indeterminate, and transient for one (0.9%) subject each. None of the subjects with treatment-emergent ADA tested positive for nAb.

***Reviewer's Comments***

(1) *The geometric mean trough concentration of tralokinumab was 80.5 μg/mL at Week 16 (SD 41.4 μg/mL, n=95) after tralokinumab 300 mg Q2W (administered SC) for 16 weeks, following an initial loading dose (tralokinumab 600 mg), which is consistent with the observations in other studies.*
(2) *Further interpretation of tralokinumab immune responses to concomitantly administered vaccines in adult subjects with moderate-to-severe AD is deferred to the review of clinical and the Office of Biotechnology Products.*

# 14.1.12. Population Pharmacokinetic Analysis of Tralokinumab in Patients with Moderate-to-Severe Atopic Dermatitis

## Title

Analysis of Tralokinumab Pharmacokinetic Data From Healthy Subjects, Subjects With Asthma, and Subjects With Atopic Dermatitis

## Objectives

The primary objectives of this population pharmacokinetic analysis were i) to quantitatively characterize the PK of tralokinumab in subjects with AD using nonlinear mixed effect analysis, and ii) to identify sources of variability in the population(s) using covariate analysis.

## Data

Tralokinumab serum concentration-time data collected from 10 clinical trials, comprising three Phase 1 trials (CAT-354-0703, MI-CP224, and CAT-354-0602), four Phase 2 trials (MI-CP199, CD-RI-CAT-354-1049, D2213C00001, and ECZTRA-5) and three Phase 3 trials (ECZTRA-1, ECZTRA-2, and ECZTRA-3), were used for the population PK analysis of tralokinumab in healthy subjects, subjects with asthma, and subjects with AD following intravenous or subcutaneous administration. The combined dataset included 13,361 serum concentrations of tralokinumab from 2,561 subjects.

## Methods

Tralokinumab serum samples were analyzed using a validated sandwich assay on the Gyrolab® platform. The assay was updated and revalidated during the clinical development program, resulting in varying lower limit of quantification across the trials: i) 0.3 µg/mL in trials CAT-354-0602, CAT-354-0703, MI-CP199, and MI-CP224; ii) 0.5 µg/mL in trial CD-RI-CAT-354-1049; and iii) 0.1 µg/mL in trials D2213C00001, ECZTRA-1, ECZTRA-2, ECZTRA-3, and ECZTRA-5.

Population PK modeling of tralokinumab was performed using a nonlinear mixed effect modeling approach in NONMEM v. 7.4. The impact of intrinsic and extrinsic covariates on PK parameters were investigated using an automated stepwise covariate modeling approach with forward selection ($P<0.01$) and backward exclusion ($P<0.001$). Subsequently, all covariates found to be statistically significant during the stepwise covariate modeling approach were evaluated for clinical relevance using a defined set of criteria. The covariates considered for the analysis were demographic factors (age, sex, body weight, race, and ethnicity), disease status (healthy, asthma, or AD), disease severity (baseline EASI score), and trial-related factors (concentration of drug formulation and ECZTRA trials versus other [‘non-ECZTRA’] trials). The predictive performance of the final popPK model was evaluated by generation of goodness-of-fit diagnostic plots, visual predictive checks, and statistical significance (objective function value).

## Results

The PK of tralokinumab in healthy subjects, subjects with asthma, and subjects with AD was adequately described using a 2-compartment model with first-order absorption and elimination (Figure 35). The systemic clearance and the volume of distribution ($V_2$+$V_3$) were estimated to be 0.149 L/day and 4.15 L, respectively. The interindividual variability for CL and $V_2$, expressed as the coefficient of variation, was 31.3% and 40.1%, respectively. Body weight, non-ECZTRA trials, and concentration of drug formulation were found to be statistically significant and clinically relevant predictors of tralokinumab exposure (Table 64). The impact of body weight was a less than two-fold difference in exposure, expressed as individually predicted AUC from Weeks 14 to 16, between the upper and lower weight quartiles for subjects in the ECZTRA trials. Goodness-of-fit plots demonstrated appropriate description of the observed data (Figure 36).

**Table 64. Final Population PK Model PK Parameter Estimates**

| Parameter | Unit | Estimate[a] | RSE (%)[b] | 95% CI[c] | Shrinkage (%) |
|---|---|---|---|---|---|
| **PK (pharmacokinetic) parameter** | | | | | |
| $k_a$ (absorption rate constant) | $day^{-1}$ | 0.184 | 4 | 0.164 – 0.202 | - |
| $V_2$ (central volume of distribution) | L | 2.71 | 7 | 2.33 – 3.00 | - |
| CL (clearance) | L/day | 0.149 | 5 | 0.136 – 0.164 | - |
| $V_3$ (peripheral volume of distribution) | L | 1.44 | 6 | 1.21 – 1.71 | - |
| Q (inter-compartmental clearance) | L/day | 0.159 | 8 | 0.125 – 0.199 | - |
| F (bioavailability) | unitless | 0.761 | 5 | 0.697 – 0.831 | - |
| o additive | µg/mL | 0.238 | 18 | 0.123 – 0.366 | - |
| o proportional | CV | 0.216 | 1 | 0.207 – 0.224 | - |
| **IIV (inter-individual variability)[d]** | | | | | |
| IIV on $V_2$ | CV% | 40.1 | 4 | 34.4 – 48.5 | 27 |
| IIV on CL | CV% | 31.3 | 2 | 29.6 – 33.0 | 7 |
| IIV on $V_2$:CL | Corr. | 0.61[e] | - | - | - |
| **Covariate** | | | | | |
| $V_2$ and $V_3$ ~ Weight | unitless | 0.783 | 4 | 0.727 – 0.842 | - |
| CL and Q ~ Weight | unitless | 0.873 | 3 | 0.816 – 0.930 | - |
| CL ~ non-ECZTRA trials | unitless | 0.344 | 6 | 0.308 – 0.387 | - |
| $V_2$ ~ non-ECZTRA trials | unitless | 0.258 | 12 | 0.198 – 0.327 | - |
| F ~ Dilution[f] | unitless | 0.354 | 19 | 0.220 – 0.499 | - |
| $k_a$ ~ Dilution[f] | unitless | -0.519 | 9 | -0.605 – -0.394 | - |

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

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

[c] 95% CI (confidence interval) was obtained from bootstrap (1000 samples and stratified on STUDY).

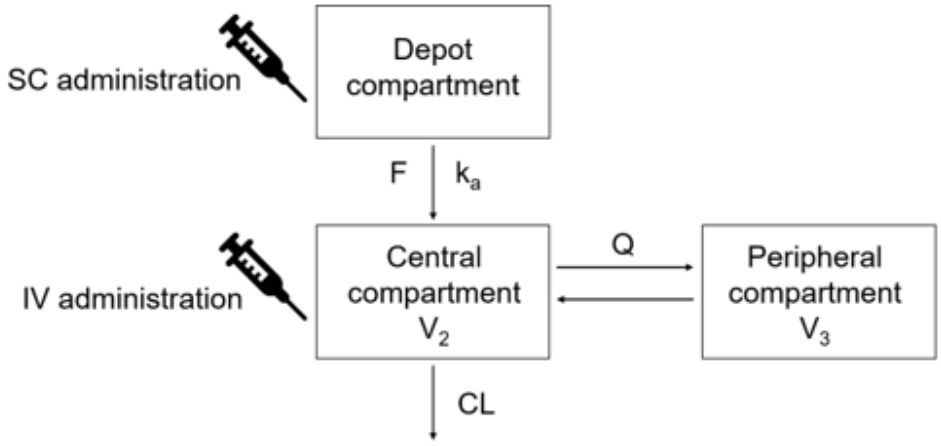
[d] IIV (inter-individual variability) was calculated as $\sqrt{(e^{\omega^2}-1)}$.

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

[f] In the 45 mg dose group of trial D2213C00001, tralokinumab was diluted before subcutaneous administration. In all other trials with subcutaneous administration, tralokinumab was injected undiluted (see Section 3.4).

Source: Module 5.3.3.5 Population Pharmacokinetic Analysis report, Tralokinumab in Moderate-to-Severe Atopic Dermatitis, Panel 13.

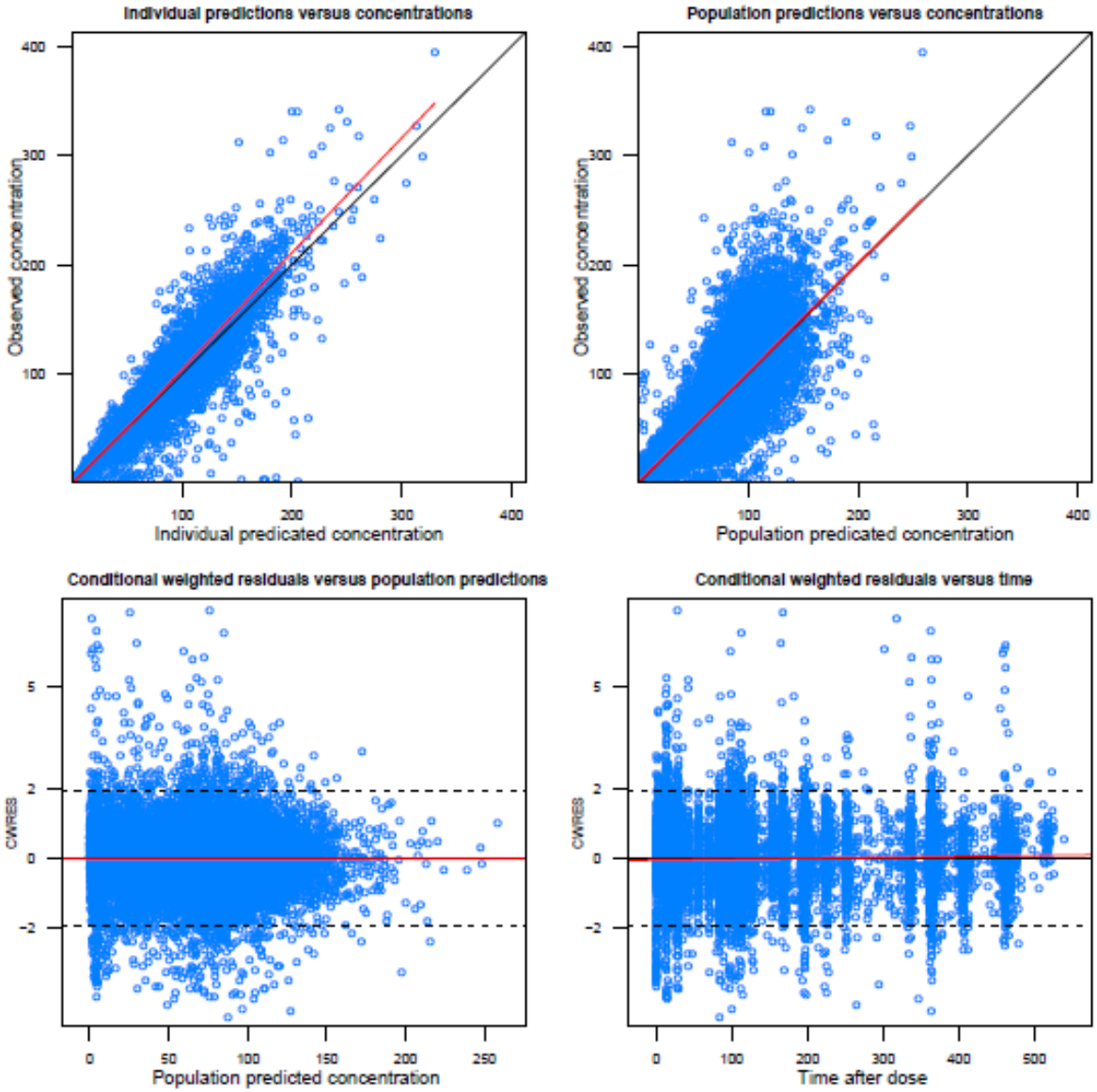
**Figure 35. Schematic of the Population Pharmacokinetics Model for Tralokinumab**




**Abbreviations:** CL = clearance; F = bioavailability; IV = intravenous; $k_a$ = absorption rate constant; Q = inter-compartmental clearance; SC = subcutaneous; $V_2$ = central volume of distribution; $V_3$ = peripheral volume of distribution.

Source: Module 5.3.3.5 Population Pharmacokinetic Analysis report, Tralokinumab in Moderate-to-Severe Atopic Dermatitis, Panel 2.

**Figure 36. Goodness-of-Fit Plot of the Final Model**




Source: Reviewer's Analysis to Confirm Figure 16 in the Applicant's Population Pharmacokinetics Report.
Top left: Correlation between the dependent variable (tralokinumab serum concentration) and the individual predictions.
Top right: Correlation between the dependent variable (tralokinumab serum concentration) and the population predictions.
Bottom left: Correlation between the conditional weighted residuals and the population predictions.
Bottom right: Correlation between the conditional weighted residuals and time.
Black circles represent the individual observations/predictions/conditional weighted residuals; red line is the trend line (LOESS).

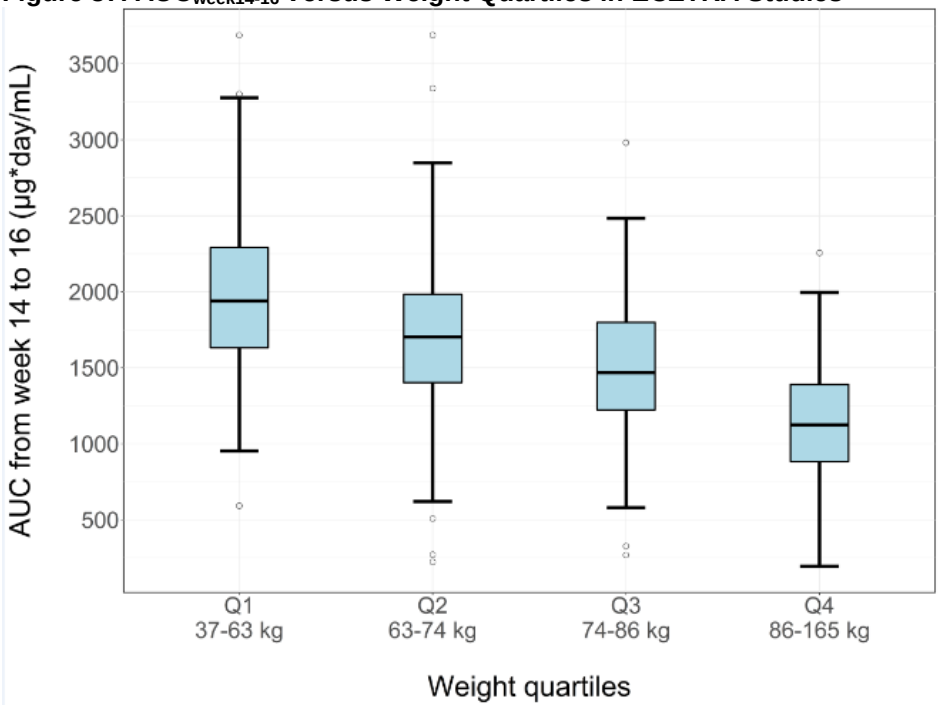
## Conclusions

Tralokinumab PK was adequately described by a 2-compartment model with first-order absorption and elimination. Interindividual variability of the PK parameters was moderate. Body weight, non-ECZTRA trials, and concentration of drug formulation were found to be statistically significant and clinically relevant predictors of tralokinumab exposure. Because both non-ECZTRA trials and concentration of drug formulation are extrinsic factors related to the

drug development process, these covariates do not have any relevance for the future clinical use of the tralokinumab 150 mg/mL solution.

The influence of body weight on exposure, expressed as simulated $AUC_{Week14-16}$, was investigated using the final popPK model (Figure 37).

**Figure 37. $AUC_{week14-16}$ Versus Weight Quartiles in ECZTRA Studies**

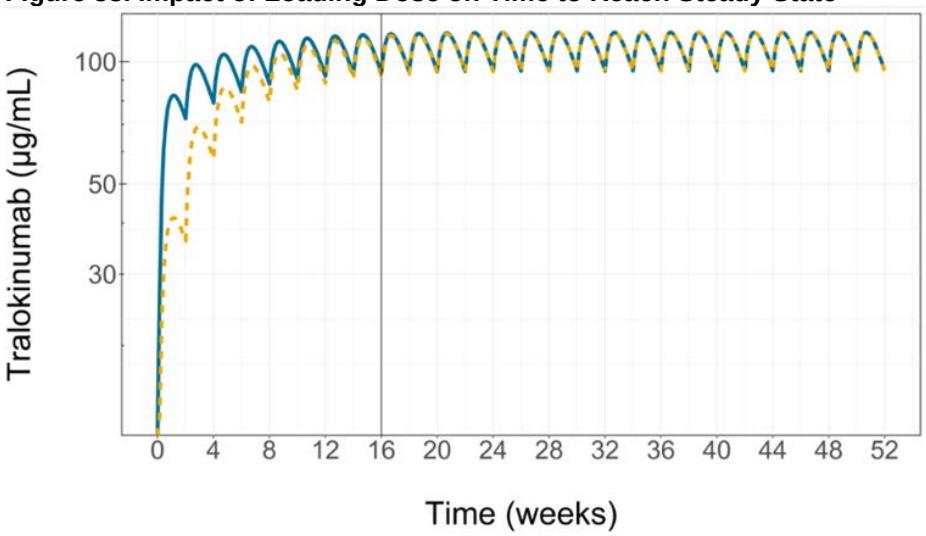



Source: Reviewer's analysis to confirm Panel 15 in the Applicant's popPK report.
Abbreviations: AUC, area under the concentration–time curve; ECZTRA, ECZema TRAlokinumab; Q, quarter

As indicated in Figure 37, there is a clear correlation between $AUC_{Week14-16}$ and weight, and a less than two-fold difference between the median of Q1 (1941 µg × day/mL) and Q4 (1125 µg × day/mL) of the overall variability was seen for exposure.

The loading dose impact on the time to reach steady state is shown in Figure 38. Based on the simulation conducted 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 reached at Week 6 *with* a loading dose and at Week 10 *without* a loading dose. Accumulation of tralokinumab following multiple dosing was predicted to be 3-fold without a loading dose and 1.5-fold with a loading dose.

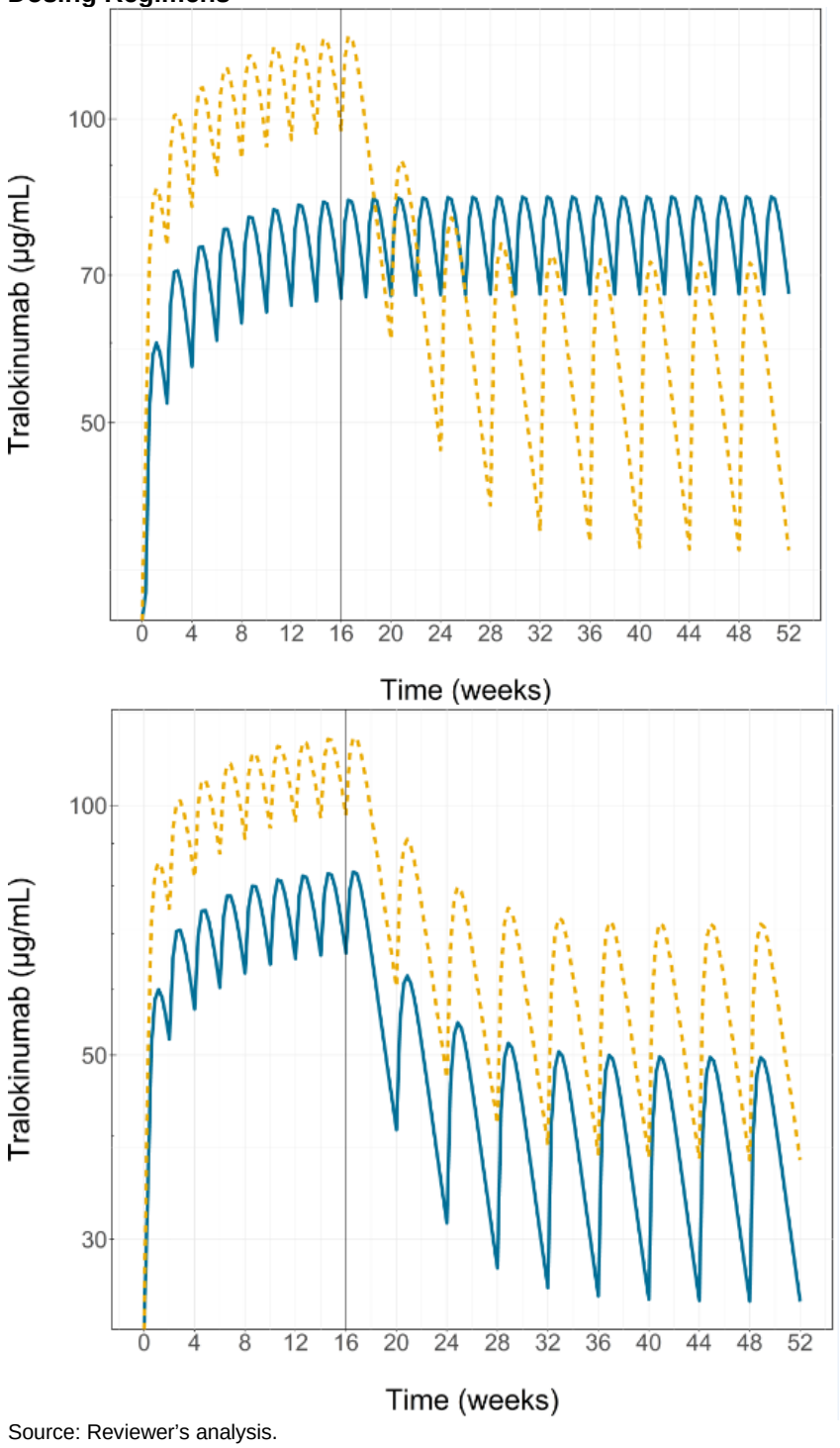
**Figure 38. Impact of Loading Dose on Time to Reach Steady State**




Source: Reviewer's plot based on the final popPK model for a typical subject with body weight at 75 kg to confirm Figure 16 in Applicant's Population PK report.

Additional PK simulations were conducted by the reviewer to investigate the drug exposure differences following varying dosing regimens in typical subjects in ECZTRA trials with representing body weight, namely a typical subject with a median body weight of 72 kg for the subject group ≤100 kg, and a typical subject with a median body weight of 111 kg for the subject group >100 kg. The typical 111 kg subject following tralokinumab 300 mg Q2W for 52 weeks demonstrated higher drug exposure after Week 16 compared to the typical 72 kg subject with tralokinumab 300 mg Q2W for 16 weeks followed by tralokinumab 300 mg Q4W until Week 52 (upper plot of Figure 39). When both typical subjects of different body weights dosed with the same dosing regimen, namely tralokinumab 300 mg Q2W for 16 weeks followed by tralokinumab 300 mg Q4W until Week 52, the typical 111 kg subject exhibited lower drug exposure after Week 16 compared to the typical 72 kg subject (lower plot of Figure 39).

**Figure 39. Simulation of Tralokinumab PK for Subjects With Typical Bodyweights at Varying Dosing Regimens**




Source: Reviewer's analysis.
Top: Simulation of the concentration–time profiles of a typical subject (weight 111 kg, solid blue line) following tralokinumab 300 mg Q2W for 52 weeks and another typical subject (weight 72 kg, yellow dashed line) with tralokinumab 300 mg Q2W for 16 weeks followed by tralokinumab 300 Q4W until Week 52.
Bottom: Simulation of the concentration–time profile for a typical subject (weight 111 kg, solid blue line) and another typical subject (weight 72 kg, yellow dashed line) dosed with tralokinumab 300 mg Q2W for 16 weeks followed by tralokinumab 300 Q4W until Week 52. Derived from the final population PK model.

***Reviewer's Comments***

(1) *This reviewer investigated the combined datasets, ran the basic structure model and final covariate model, and confirmed the PK parameter estimates.*
(2) *The final popPK model provided an adequate description of the observed concentration–time profiles of tralokinumab in subjects with AD, in healthy subjects as well as subjects with asthma following IV and SC administration.*
(3) *Body weight was identified as the only clinically meaningful covariate identified on tralokinumab exposure. The exposure of tralokinumab decreases with increasing body weight. Individually predicted AUC from Weeks 14 to 16 in ECZTRA trials demonstrated a less than two-fold difference in exposure between the upper and lower body weight quartiles. The effect of body weight was further assessed in the context of tralokinumab efficacy and safety in the exposure-response (ER) analysis.*
(4) *In the trials with tralokinumab completed to date, the incidence of ADA was low (below 5%) and there was no indication of any impact of ADA on the observed PK of tralokinumab from individual ECZTRA trials. ADA was not evaluated as a covariate in the popPK analysis.*

## 14.1.13. Exposure–Response Analysis of Tralokinumab in Moderate-to-Severe Atopic Dermatitis

### Title

Exposure-Response Analysis of Relationship Between Systemic Exposure of Tralokinumab and Efficacy and Safety Data From Adult Subjects With Moderate-to-Severe Atopic Dermatitis

### Objectives

- Investigate the relationship between efficacy and systemic exposure of tralokinumab when administered as a monotherapy.
- Investigate the relationship between conjunctivitis (identified as an AESI) and systemic exposure of tralokinumab.

### Data

Exposure data and selected response data up to Week 16 from the Phase 3 trials ECZTRA-1 and -2 (monotherapy pool) and ECZTRA-3 (tralokinumab–TCS combination trial) (Table 65) were included in the analyses.

**Table 65. Trials with Tralokinumab in Subjects with AD Included in ER Analyses**

| Trial ID, link | Phase, type, duration | Dose, route, regimen (planned number of subjects) | PK sampling (Week) | EASI/IGA assessment |
|---|---|---|---|---|
| ECZTRA 1<br>M5.3.5.1 ECZTRA 1 CTR | Phase 3<br>Multiple dose<br>(52 weeks, 26 doses) | Tralokinumab 300 mg SC Q2W (n=585)<br>Placebo SC Q2W (n=195)<br>After Week 16, subjects could be re-randomised to placebo, Q2W or Q4W | 2, 4, 14, 15, 16, 28, 52, 66[a] | Q2W (Week 0-52) |
| ECZTRA 2<br>M5.3.5.1 ECZTRA 2 CTR | Phase 3<br>Multiple dose<br>(52 weeks, 26 doses) | Tralokinumab 300 mg SC Q2W (n=585)<br>Placebo SC Q2W (n=195)<br>After Week 16, subjects could be re-randomised to placebo, Q2W or Q4W | 2, 4, 16, 28, 52, 66 | Q2W (Week 0-52) |
| ECZTRA 3<br>M5.3.5.1 ECZTRA 3 CTR | Phase 3<br>Multiple dose<br>(32 weeks, 16 doses) | Tralokinumab 300 mg SC Q2W + TCS (n=253)<br>Placebo SC Q2W + TCS (n=127)<br>After Week 16, subjects could be re-randomised to Q2W or Q4W | 4, 16, 32 | Q2W (Week 0-32) |

[a] In Japanese subjects, a sample was planned to be taken at Week 68 and a final sample was planned at Week 82 if the subject was not transferred to long-term extension trial (LP0162-1337).

**Abbreviations**: AD = atopic dermatitis; EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous; TCS = topical corticosteroid.

Source: Module 5.3.4.2 Exposure–response analysis report, tralokinumab in moderate-to-severe atopic dermatitis, Panel 1

The analysis datasets consisted of subjects in the tralokinumab 300 mg Q2W or in the placebo groups who:

- Completed treatment to Week 16.
- Completed treatment to Week 16.
- Did not receive rescue treatment before or at Week 16.
- Had an efficacy response (EASI) recorded at Week 16.
- Had a quantifiable serum concentration measurement at Week 16 (only applicable for subjects in the tralokinumab 300 mg Q2W group).

These criteria were used for the monotherapy pool (ECZTRA-1 and -2) and for ECZTRA-3.

## Methods

The monotherapy trials were considered to provide the most appropriate data to investigate the tralokinumab exposure-efficacy relationship. The tralokinumab+TCS combination trial, ECZTRA-3, was used for the purpose of sensitivity analysis only. The Applicant conducted two different types of analyses: quartile and nonlinear mixed effect (NLME) model analyses. The reviewer conducted logistic regression based on ER data created by the Applicant.

In the quartile analysis, efficacy responses (% change from baseline in EASI score [ΔEASI%] and proportion of IGA 0/1 responders) were stratified in terms of quartiles of steady state exposure (observed $C_{trough}$ at Week 16 and model-predicted $AUC_{0\text{-}W16}$) and body weight.

In the ER model (NLME), exposure metrics (observed steady state $C_{trough}$ and model-predicted $AUC_{0\text{-}W16}$) were used as independent variables and ΔEASI% as the response variable. The following continuous and categorical covariates were tested in the model: body weight, sex, age, race, and disease severity (baseline EASI score).

In the ER model (NLME), exposure metrics (observed steady state $C_{trough}$ and model-predicted $AUC_{0\text{-}W16}$) were used as independent variables and ΔEASI% as the response variable. The following continuous and categorical covariates were tested in the model: body weight, sex, age, race, and disease severity (baseline EASI score).

In the quartile analysis of the ER relationship related to safety, AESIs (conjunctivitis) were assessed against quartiles of steady state exposure (observed $C_{trough}$ at Week 16 and model-predicted $AUC_{0\text{-}W16}$). The analysis was performed on the monotherapy pool only as this pool was considered to provide the best foundation for detecting a relationship.

In the logistic regression ER model, exposure metrics (observed $C_{trough}$ at Week 16) were used as independent variables and the probability of patients achieving an IGA score of 0 or 1 (IGA 0/1) and a reduction of 75% in EASI score from baseline (EASI-75) as response variables. The following continuous and categorical covariates were tested in the model: body weight, sex, age, race, and disease severity (baseline EASI score).

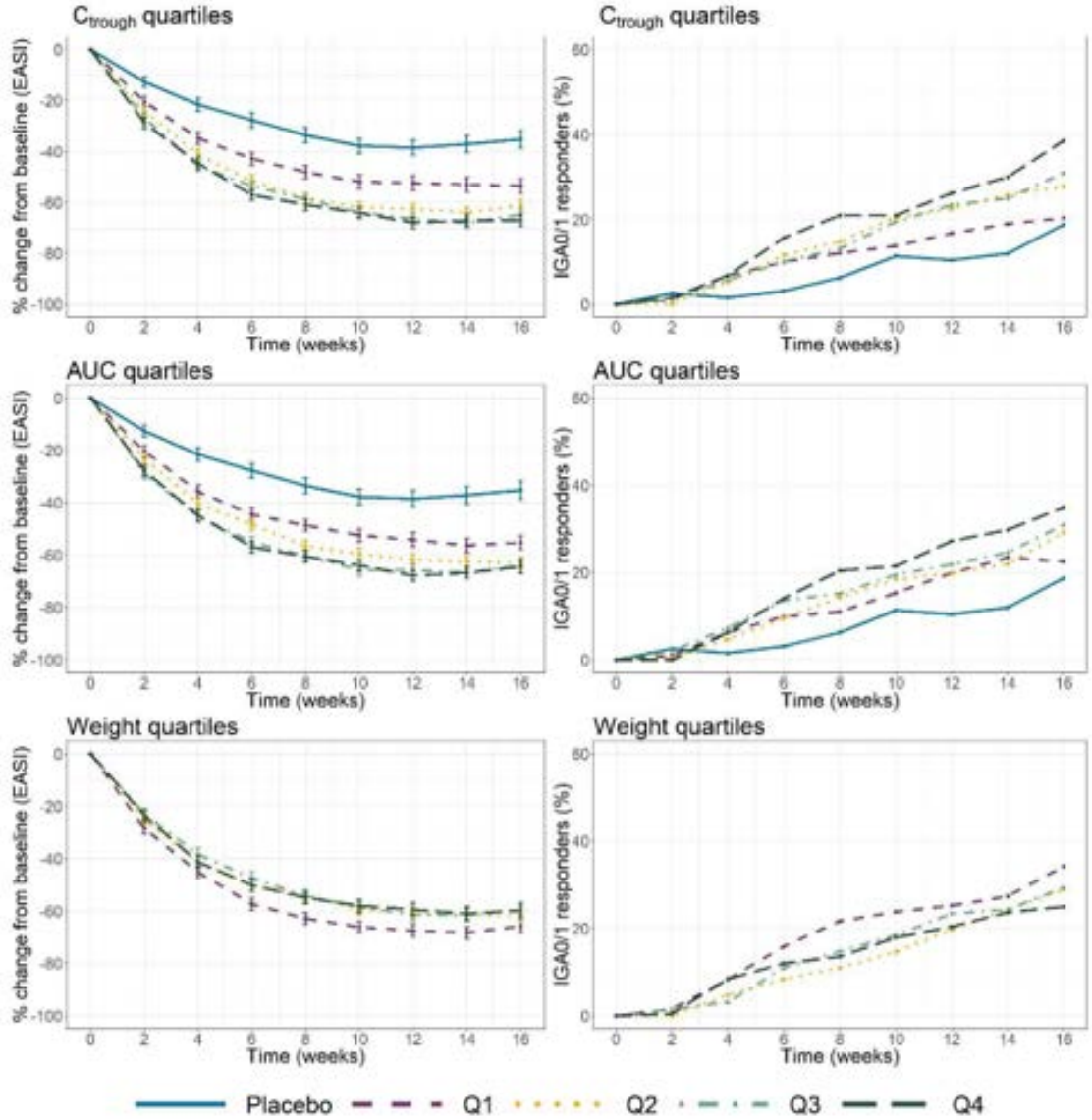
The Applicant's analyses were performed using R v. 3.4.2 and NONMEM v. 7.4.3 with auxiliary software. The reviewer's analyses were conducted using R v. 3.6.3 and NONMEM v. 7.4.3.

## Results

In the quartile analysis of exposure versus efficacy in the monotherapy trials, a clear relationship was observed between exposure ($C_{trough}$ at Week 16 and $AUC_{0\text{-}W16}$) and efficacy (EASI and IGA response) (Figure 40). At Week 16, the subjects within the lowest exposure quartile had the lowest response, and the subjects within the highest exposure quartile had the highest response. For the EASI variable, this trend also included the intermediate quartiles, and the ER relationship was evident at all visits in the initial treatment period.

Body weight has been identified as a significant predictor of tralokinumab exposure, indicating that subjects with a lower body weight have a higher exposure of tralokinumab at steady state than subjects with a higher body weight (Figure 39). Likewise, stratification of individual $C_{trough}$ values (at Week 16) by body weight showed that $C_{trough}$ decreased with increasing body weight quartile. 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.

**Figure 40. EASI and IGA Responses From Weeks 0 to 16 Stratified by Quartiles of Tralokinumab Trough Concentration, Model-Predicted AUC, and Bodyweight**




Source: Module 5.3.4.2 Exposure–response analysis report Tralokinumab in moderate-to-severe atopic dermatitis, Panel 14
Percentage change from baseline in EASI score is given as mean ± standard error of the mean; IGA 0/1 responders are defined as subjects with an IGA score of 0 (clear) or 1 (almost clear); AUC is individually predicted from Weeks0-16 based on population pharmacokinetic modelling; $C_{trough}$ is the observed trough concentration at Week 16.
Abbreviations: AUC, area under the serum concentration–time curve from time zero to Week 16; $C_{trough}$, observed trough concentration; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; Q, quartile

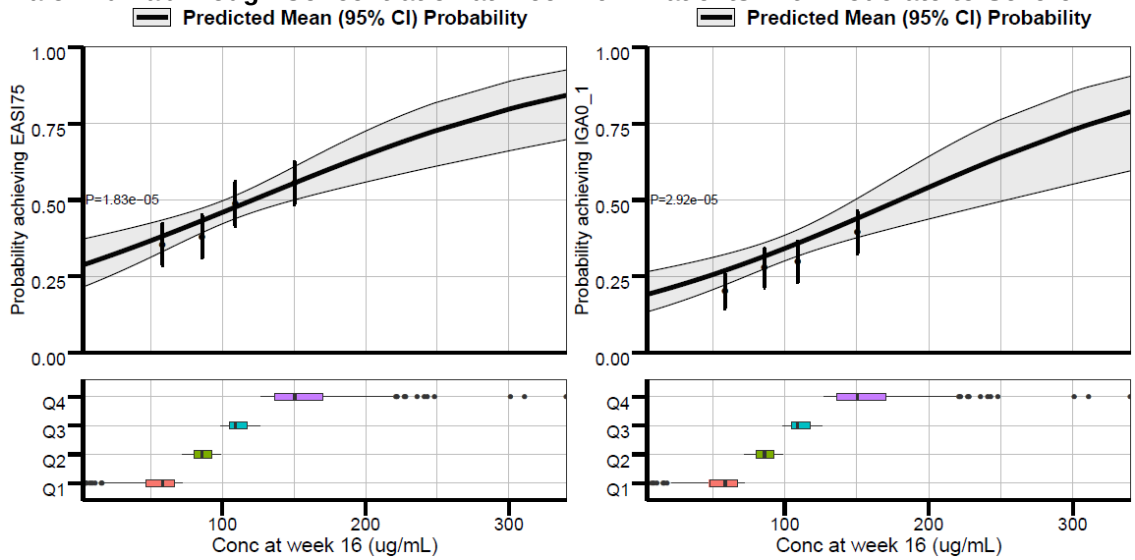
In the quartile analysis of ECZTRA-3, which included concomitant TCS treatment, a relationship between tralokinumab exposure and reduction in EASI score was observed.

In the quartile analysis of the ER relationship assessing the incidence of conjunctivitis versus exposure, 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.

In the NLME ER modeling approach assessing efficacy versus exposure, an $E_{max}$ model was found to provide the best description of the relationship between efficacy and steady state tralokinumab exposure. For the typical subject (non-black or black/African-American and baseline EASI score of 25), the placebo effect E0 was estimated to -31.4% and the steady-state $C_{trough}$ exposure estimated to achieve half of the maximum treatment response was 37.8 µg/mL. Maximum response, $E_{max}$, was estimated at -88.9%. Race was found to have a significant effect on the ER relationship, consistent with a higher placebo response in the black/African-American population than in non-black populations. Baseline EASI score was also found to have a significant effect on the ER relationship, 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.

In the logistic ER modeling approach investigating tralokinumab exposure (observed steady-state $C_{trough}$) versus probability of patients achieving an IGA score of 0 or 1 (IGA 0/1) and at least a 75% reduction in EASI score from baseline (EASI-75) at Week 16, the percentage of patients achieving IGA 0/1 and EASI-75 is higher in higher tralokinumab steady state concentration quartiles. The final logistic regression models also identified race as significant covariate on IGA (0,1), and race and disease severity (baseline EASI total score) as significant covariates on EASI-75 (Figure 41), which is consistent with the NLME ER modeling results on EASI-75 conducted by the Applicant.

**Figure 41. Logistic Regression of Probability of Achieving EASI-75 (Left) and IGA (0,1) (Right) to Tralokinumab Trough Concentration at Week 16 in Patients With Moderate-to-Severe AD**




Source: Reviewer's analysis.
Mean regression line—black, confidence area around regression line—grey. The p-value represents the statistical significance of the inclination of the regression line. Means of response variables (black circles) and confidence intervals (black vertical lines) around the means are presented in the figures by quartile of exposure.

## Conclusion

Based on the Week 0 to 16 data, the quartile analysis, as well as the model-based NLME and logistic regression of tralokinumab ER for the 300 mg Q2W dosing regimen, identified a clear ER relationship between tralokinumab exposure (steady state $C_{trough}$ and AUC) and the observed efficacy responses (ΔEASI%, achieving IGA 0/1, and a reduction of EASI-75 at Week 16). Of the covariates tested in the ER modeling (monotherapy) approaches, race (non-black and

black/African-American) and disease severity (baseline EASI score) were found to affect the tralokinumab ER relationship. No relationship between quartiles of exposure and the incidence of conjunctivitis was observed.

***Reviewer's Comments***

(1) *The quartile analyses, as well as the model-based NLME and logistic regression of tralokinumab ER for the 300 mg Q2W dosing regimen, identified a clear ER relationship between tralokinumab exposure (steady state $C_{trough}$ and/or AUC) and the observed efficacy responses, namely ΔEASI%, achieving IGA 0/1 and reduction of EASI-75 at Week 16.*

(2) *Given tralokinumab was administered as a flat dose to all participants in ECZTRA trials in the initial treatment from Weeks 0 to 16, bodyweight stratified quartile ER relationships could be confounded by the factor that higher bodyweight subjects got decreased tralokinumab exposure.*

(3) *Based on both NMLE and logistic regression model-based ER analyses, body weight was not identified as a significant covariate affecting tralokinumab drug efficacy.*

## 14.1.14. Summary of Biomarker Analysis for Pivotal Study LP0162-1325 (ECZTRA-1)

### Serum Biomarkers

The results presented for serum biomarkers were measured in the pivotal Phase 3 trial, LP0162-1325 (ECZTRA-1) in AD. All subjects had blood samples taken for analysis of a small panel of biomarkers. These samples were taken at Weeks 0, 4, 8, 16, 28, and 52 according to the schedules of trial procedures. The biomarkers: periostin, DPP-4, hBD2, CCL17, IL-13, IL-17, IL-22, and IgE were analyzed.

**Small Panel Biomarkers**

Serum was prepared by gently mixing the blood by inverting the tube and allowing blood to clot with the tube in an upright position at room temperature for 30 min, followed by centrifugation for 10 min at 1800 g. The serum was transferred equally to 4 × 2 mL cryovial tubes and frozen immediately. The frozen samples were stored at -70°C (storage at -20°C was permitted only if no ultracold freezer was available) and transferred to a central laboratory for storage at -70°C until analysis.

Blood samples from 300 randomly selected patients from LP0162-1325 were analyzed for key serum biomarkers. This set of markers is referred to as "small panel biomarkers." The biomarkers included in the small panel biomarkers are listed in Table 66.

**Table 66. Small Biomarker Analytes**

| Analyte | Assay format | Lower level of quantification | Assay ID |
|---|---|---|---|
| Periostin | ELISA | 82 pM | Thermofisher, cat. # EHPOSTN |
| DPP4 | ELISA | 25 pg/mL | Thermofisher, cat. # EHDPP4 |
| CCL17 | ELISA | 31.2 pg/mL | R&D Systems, cat. # DDN00 |
| hBD-2 | ELISA | 3.2 pg/mL | Creative Diagnostics, cat. # DEIA7824 |
| IL-13 | Erenna Singulex | 0.02 pg/mL | EMD Millipore, cat. # 03-0109 |
| IL-17 | Quanterix single molecule detection | 0.02 pg/mL | Simoa IL-17A SR-X |
| IL-22 | Erenna Singulex | 1.6 pg/mL | EMD Millipore, cat. # 03-0059 |

Source: Panel 4, 5.3.5.1 Biomarker Analysis Report_Study lp0162-1325 Report Body
Abbreviations: ELISA, enzyme-linked immunosorbent assay; CCL, CC chemokine ligand; DPP-4, dipeptidyl peptidase 4; hBD-2, human β-defensin 2; IL, interleukin

Each assay used for analysis of the small panel biomarkers underwent a fit-for-purpose validation. The following assay validation parameters were investigated for each method:

- Standard curve and curve fitting
- Precision and accuracy
- Selectivity (spiked recovery)
- Dilutional linearity/parallelism
- Maximum batch size and assay drift
- Short-term and freeze thaw stability
- Intermediate stability (1 month at -70°C)
- Long-term stability up to 12 months at -70°C
- Run acceptance criteria

## Large Panel Biomarkers

A subgroup of subjects consented to have additional serum samples collected for further biomarker exploration. For this analysis, a multiplex-based Meso scale discovery VPLEX assay (cat. No. K15054D) was used, and a total of 30 inflammatory markers was measured. The analytes constitute what is referred to as “the large panel biomarker”, and the analytes are presented in Table 67.

**Table 67. Large Panel Biomarker Analytes**

| Analyte | Assay range (pg/mL) | Analyte | Assay range (pg/mL) |
|---|---|---|---|
| IFN-γ | 0.20–938 | IL-15 | 0.17–525 |
| IL-1β | 0.04–375 | IL-16 | 2.83–1875 |
| IL-2 | 0.09–93 | IL-17A | 0.74–3653 |
| IL-4 | 0.02–158 | TNF-β | 0.05–458 |
| IL-6 | 0.06–488 | VEGF | 1.12–784 |
| IL-8 | 0.04–375 | CCL26 (Eotaxin-3) | 3.26–1120 |
| IL-10 | 0.03–233 | CCL4 (MIP-1β) | 0.37–750 |
| IL-12p70 | 0.11–315 | CCL26 (Eotaxin-3) | 1.77–3750 |
| IL-13 | 0.24–353 | CCL17 (TARC) | 0.22–1120 |
| TNF-α | 0.04–248 | CXCL10 (IP-10) | 0.37–500 |
| GM-CSF | 0.14–750 | CCL3 (MIP-1α) | 3.02–743 |
| IL-1α | 0.09–278 | IL-8(HA) | 95.6–43 400 |
| IL-5 | 0.22–562 | CCL2 (MCP-1) | 0.09–375 |
| IL-7 | 0.16–563 | CCL22 (MDC) | 1.22–7500 |
| IL-12/IL-23p40 | 0.39–2250 | CCL13 (MCP-4) | 1.69–469 |

Source: Panel 5, 5.3.5.1 Biomarker Analysis Report_Study lp0162-1325 Report Body
Abbreviations: IFN, interferon; IL, interleukin; CCL, CC chemokine ligand; CXCL, chemokine (C-X-C motif) ligand; GM-CSF, granulocyte-macrophage colony-stimulating factor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor

## Skin Biopsies

Subjects were invited to donate skin biopsies to be used for measurement of protein expression by immunohistochemistry (IHC) and gene expression by quantitative polymerase chain reaction (qPCR) and RNA sequencing. Fifty subjects (of 100 subjects who were asked) consented to donate skin biopsies for this purpose. Four skin biopsies of 3 mm diameter were obtained from each trial subject. These samples comprised Visit 3 nonlesion (baseline), Visit 3 lesion (baseline), Visit 5 (4 weeks; lesion), and Visit 12/End of Trial (16 weeks; lesion).

Skin biopsies for IHC were submerged in 10% neutral buffered formalin and shipped to (b) (4) at ambient temperature. Samples were tissue-processed and paraffin-embedded within 7 days of fixation. When all biopsies had been collected and paraffin embedded at (b) (4), the tissue was shipped to LEO Pharma A/S at ambient temperature.

Skin biopsies for RNA analysis were transferred to a vial containing RNALater solution (1.5 mL). The vial was placed at 2 to 8°C for 16 to 30 hr and stored at -20°C to -80°C until shipment on dry ice.

### Immunohistochemistry and Histology Analysis of Skin Biopsies

*Processing and Staining*

Biopsies were re-embedded so that all biopsies from the same subject were placed in one paraffin block. The location of the biopsies in the block was randomized according to visit and lesional/nonlesional status. The blocks were sectioned at 5 μm for Masson's trichrome staining and at 3 μm for all other staining. Tissue sections were stained by IHC for the large panel markers. Heat-induced epitope retrieval was performed overnight at 60°C, pH 9. Sections were stained on an automated BOND RX Stainer (Leica Biosystems) using the J protocol, which has Fast red as chromogen (BOND Polymer Red Refined Kit). Nuclei were stained blue with hematoxylin.

*Quantification of Staining*

The stained slides were scanned with a Nanozoomer 2.0 HT (Hamamatsu) slide scanner at 20×. The amount of staining was quantified by whole slide digital image analysis using Visiopharm Integrator Software by a blinded observer. To confirm the specificity of the individual antibody staining for each biomarker analysis, 21 to 106 sections were stained with a corresponding isotype control antibody as negative controls. Hair follicles were excluded from analysis when markers were analyzed in epidermis alone.

**Targeted Gene Expression Analysis of Skin Biopsies (qPCR)**

*RNA Extraction and Quality Control*

RNA was isolated using the miRNeasy Mini Kit (Qiagen), following the manufacturer's instructions. On-column DNase digestion was performed during the RNA extraction. The RNA concentration was determined using the Qubit 2.0 fluorometer (Thermo Fisher Scientific). On average, an RNA concentration of 136.2 ng/µL was obtained, ranging from 0 to 467.2 ng/µL. RNA quality control was performed using the Fragment Analyzer Automated Capillary Electrophoresis System (Advanced Analytical). The complete absence of genomic DNA (gDNA) could be confirmed for almost all samples. Analytical details as well as samples lists, RNA concentrations, and quality scores are provided in the analytical report.

*Gene Expression Analysis by qPCR*

Complementary DNA (cDNA) synthesis was performed using the iScript Advanced cDNA Synthesis Kit (Bio-Rad) with 50 ng of total RNA as input, unless specified otherwise in the analytical plan. The cDNA quality of each sample was assessed by means of two universally expressed genes.

Prior to cDNA quantification, a gene-specific PCR-based preamplification step consisting of 12 cycles was performed to ensure sufficient template for reliable quantification. Sample preamplification was conducted in a reaction volume of 50 µL using PreAmp Supermix (Bio-Rad). Unless specified otherwise in the analytical plan, a total of 12.5 ng cDNA (total RNA equivalents) was used as input in each preamplification reaction. The preamplified cDNA product was diluted 1:20 prior to gene expression profiling.

For gene expression profiling, we used validated approaches for qPCR amplification. All measurements were performed in 384-well plates (CFX384, Bio-Rad) in a reaction volume of 5 µL, using SYBR Green I. Each PCR reaction was conducted in duplicate; 2 µL of the 1:20 diluted PreAmp was used as input in each PCR reaction.

qPCR Data analysis was performed according to the methods in AP_CT2019_002_v1.0 and corresponding amendments using Biogazelle's qbase+ (http://www.qbaseplus.com). This software is built upon a state-of-the-art and heavily cited quantification model (Hellemans et al. 2007), including PCR efficiency correction, multiple reference gene normalization or global mean normalization, inter-run calibration and error propagation, and offers numerous tools for quality control.

## Analysis of *S. aureus* Colonization in Lesional Skin

### Sampling

All subjects on LP0162-1325 had skin swabs collected from lesional skin areas for analysis of the abundance of *S. aureus* at baseline and at Weeks 16 and 52. In a subset of patients, swabs were also collected for analysis of the skin microbiome by DNA sequencing. These extra swabs were collected at baseline, and at Weeks 8, 16, and 52.

Swab samples were taken from skin areas of 5 × 10 cm. The swab was rubbed gently across the whole skin area for about 1 min. The swab tip back was moved back and forth and rolled to allow all hairs on the swab to contact the skin area. The swab was returned to its plastic container, sealed, and stored at <-20°C, preferably <-70°C, until shipment.

### Processing

The swabs were thawed at room temperature. Each of the swabs was clicked into a slic-prep plate and 360 µL of ATL buffer and 40 µL of Proteinase K (both from Qiagen) were added. The samples were next lysed at 56°C for 1.5 hr. After lysis the plate was moved to 4°C, followed by 37°C until crystals from the buffer dissolved. The plate was next vortexed and spun for 2 min at 2000 rpm. Two-hundred microliters were transferred to Sarstedt tubes, which were transferred to the Qiasymphony robot. DNA was extracted using the DSP DNA Mini Kit (Qiagen) and the TLC_200_CR21830_ID2093 program. DNA was eluted into 50 µL of ATE buffer (Qiagen).

### qPCR

The abundance of *S. aureus* DNA was quantified using a species-specific primer set targeting *femA* (Thermo Fisher assay ID Ba04230906_s1). The specific assays of interest were pooled to a final assay concentration of 0.2× in 1× TE DNA suspension buffer. The assay pool was mixed with TaqMan PreAmp Master Mix (2×) in a relation of 1:2 to create Pre-Mix for the specific target amplification. The STA reaction was performed using the DNA samples mixed with the Pre-Mix at a ratio of 1:3 with a final volume per sample of 5 µL. The history of the PCR run was checked for exceptions in order to maintain the quality and integrity of the sample run. After the STA run, the reactions (PreAmp of samples) were diluted 1:5 using 1× TE DNA suspension buffer. The 20× TaqMan expression assays were diluted 1:1 with Assay Loading Reagent. Blank spots were diluted in the same manner using Molecular Grade Water instead of assay, as there can be no empty spots on the chip. The assays were ready at this step for Fluidigm 192.24 Chip. Sample Pre-Mix for gene expression were prepared using TaqMan Gene Expression Master Mix (2×) and 20× GE Sample loading reagent mixed in a 10:1 ratio. Final sample preparation for the chip involved mixing the sample Pre-Mix with the DNA sample PreAmp in a 1.26:1 ratio. The assays and samples were loaded to the Fluidigm 192.24 gene expression chip. To determine relative colony-forming units of *S. aureus*-specific DNA, a standard curve was generated using genomic DNA extracted from standards derived from known numbers of colony forming units of *S. aureus* (ATCC6538), and was normalized to the swabbed skin area.

# 14.2. In Vivo Studies

Not Applicable.

# 15. Trial Design: Additional Information and Assessment

This section describes the design of the three Phase 3 trials ECZTRA-1, ECZTRA-2, and ECZTRA-3, which were submitted as evidence of safety and efficacy. The monotherapy trials ECZTRA-1 and ECZTRA-2 are of identical design, and therefore, are summarized together.

## ECZTRA-1 and ECZTRA-2

ECZTRA-1 and ECZTRA-2 are two identically designed, randomized, multicenter, double-blind, placebo-controlled, monotherapy Phase 3 trials to evaluate the efficacy and safety of tralokinumab in adult subjects with AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Initial Treatment Period: The protocols specified enrolling and randomizing approximately 780 subjects from approximately 130 sites in a 3:1 ratio to receive tralokinumab 300 mg (N=585) or placebo (N=195) Q2W. Randomization was stratified by region (ECZTRA-1: North America, Europe and Japan; ECZTRA-2: North America, Europe, Australia and Asia) and baseline disease severity (IGA of 3 or 4).

Maintenance Treatment Period: beginning at Week 16, treatment during the maintenance treatment period was based on the subject's clinical response (defined as IGA 0/1 or EASI-75) at that visit.

- Subjects who achieved a clinical response at Week 16:
  - Subjects originally randomized to tralokinumab Q2W in the initial treatment period were rerandomized in a 2:2:1 ratio to:
    - Tralokinumab 300 mg Q2W
    - Tralokinumab 300 mg Q4W
    - Placebo maintenance regimens

    Randomization was stratified by region and IGA response at Week 16 (IGA 0/1 or IGA >1).
  - Subjects randomized to placebo in the initial treatment period continued to receive placebo Q2W in the maintenance treatment period.
- Subjects who did not achieve a clinical response at Week 16:
  - Subjects who did not achieve a clinical response at Week 16 were transferred to the open-label period.

Open-Label Period: Subjects who did not achieve a clinical response at Week 16, as well as those who met the following prespecified criteria indicating insufficient response during the maintenance treatment period, were transferred to open-label tralokinumab 300 mg Q2W treatment with optional use of TCS up to Week 52:

- Subjects with IGA=0 at Week 16.
  - IGA of at least 2 and not achieving EASI-75 over at least a 4-week period (i.e., over three consecutive visits) during the maintenance treatment period.
- Subjects with IGA=1 at Week 16.
  - IGA of at least 3 and not achieving EASI-75 over at least a 4-week period (i.e., over three consecutive visits) during the maintenance treatment period.
- Subjects with IGA >1 at Week 16.
  - Not achieving EASI-75 over at least a 4-week period (i.e., over three consecutive visits) during the maintenance treatment period.

Subjects transferring to open-label treatment had the option to self-administer tralokinumab or have tralokinumab administered by a caregiver in their home after adequate training by site staff and at the Investigator's discretion. Subjects who did not want to self-inject could have the staff at the trial site administer all of the injections at the trial site.

For ECZTRA-1 only, Japanese subjects who were transferred to the open-label tralokinumab arm at Week 16 continued an additional 16 weeks (Weeks 52 to 68) of open-label treatment. This group of subjects is hereafter referred to as *selected Japanese subjects*.

Safety Follow-up Period: Eligible subjects were invited to enter an open-label long-term extension trial conducted under a separate protocol (ECZTEND). Subjects who consented to transfer to ECZTEND were required to have had their last visit in the treatment period (Week 52; Week 68 for selected Japanese subjects in ECZTRA-1) and could transfer to ECZTEND at any time during the safety follow-up period. All subjects, excepting 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 and ADA.

Subjects who permanently discontinued the investigational medicinal product (IMP) prior to Week 16 were asked to attend:

- Early termination visit
- Nominal Week 16 visit (16 weeks after randomization)
- Safety follow-up visit (16 weeks after last administration of IMP)

Subjects who permanently discontinued IMP at Week 16 or after Week 16 were asked to attend:

- Early termination visit
- Safety follow-up visit (16 weeks after last administration of IMP)

### ECZTRA-3

ECZTRA-3 was a randomized, multicenter, double-blind, placebo-controlled, Phase 3 trial to confirm the efficacy and safety of tralokinumab as adjunct therapy with TCS in adult subjects with moderate-to-severe AD who are candidates for systemic therapy.

Initial Treatment Period: The protocol specified enrolling and randomizing approximately 369 subjects from approximately 70 sites in Europe and North America in a 2:1 ratio to tralokinumab 300 mg+TCS (N=246) or placebo+TCS (N=123) Q2W. Randomization was stratified by region (North America and Europe) and baseline disease severity (IGA of 3 or 4).

Continuation Treatment Period: Beginning at Week 16, treatment during the continuation treatment period was based on the subject's clinical response (defined as IGA 0/1 or EASI-75) at that visit:

- Subjects who achieved a clinical response at Week 16:
  - Subjects originally randomized to tralokinumab Q2W in the initial treatment period were rerandomized in a 1:1 ratio to:
    - Tralokinumab 300 mg Q2W
    - Tralokinumab 300 mg Q4W

    Randomization was stratified by region and IGA response at Week 16 (IGA 0/1 or IGA >1).
  - Subjects randomized to placebo in the initial treatment period continued to receive placebo Q2W in the continuation treatment period.
- Subjects who did not achieve a clinical response at Week 16:
  - Subjects who did not achieved clinical response at Week 16 received tralokinumab 300 mg Q2W in the continuation treatment period.

Safety Follow-up Period: Eligible subjects (in selected countries) had the opportunity to enter the open-label long-term extension trial, ECZTEND. Subjects who transferred to ECZTEND were required to have had their last visit in the treatment period (Week 32) and could transfer to ECZTEND at any time during the safety follow-up period. All subjects, except for those who entered the open-label long-term extension trial (ECZTEND), completed a 14-week off-treatment follow-up period for the assessment of safety and antidrug antibodies (ADA).

# 16. Efficacy: Additional Information and Assessment

## Information Regarding Removal of Sites 423, 435 (ECZTRA-2), and 818 (ECZTRA-3) from Safety and Efficacy Evaluations

On 5/12/2020, the Applicant notified the Agency that they decided to terminate clinical research activities at Site 818/ECZTRA-3 due to several concerns about good clinical practices (GCP) noncompliance and data integrity. A total of 12 subjects was randomized in Site 818. On 8/21/2020, the Applicant notified the Agency that Site 435/ECZTRA-2 was closed due to GCP

noncompliance with Investigator responsibilities for records and reports. Only two subjects were randomized in Site 435.

During site inspections, review of the regulatory history at Site 423/ECZTRA-2 showed that this site was terminated in 4/2018. A total of 20 subjects was randomized in Site 423/ECZTRA-2. The Agency requested from the Applicant copies of any communications to the Agency regarding the termination of this site or to indicate the location of such communications under the IND and/or BLA. In response, the Applicant noted that the communication with the Agency regarding the closure for Site 423 occurred under the IND.

The review team was notified by OSI regarding this matter on 11/2/2020. On 11/18/2020, the Agency sent an Information Request letter to the Applicant asking for clarification on which sites were closed in each trial along with the dates of closure, the reasons for the closure of such sites and the number of subjects in these sites, the treatment duration for each subject and efficacy and safety assessments of the closed sites. In response (11/20/2020), the Applicant reiterated Sites 423 and 435 in ECZTRA-2 and Site 818 in ECZTRA-3 were terminated. The Applicant did not indicate that any other sites were closed. The Applicant noted that Site 423/ECZTRA-2 was closed prematurely while the trial was still ongoing, due to the GCP noncompliance issues identified in relation to a site audit, while Sites 435/ECZTRA-2 and 818/ECZTRA-3 were terminated after the completion of the trials. At Site 423/ECZTRA-2 and Site 818/ECZTRA-3, the noncompliance identified by the Applicant included lack of oversight as well as inconsistencies in documentation practice for important data points such as IMP administration and protocol-mandated clinical assessments. In light of the issues noted above, the review team decided to exclude Sites 423, 435 (ECZTRA-2), and 818 (ECZTRA-3) from the evaluations of safety and efficacy. The review team otherwise concluded that the conduct of the trials appears to be adequate and the data generated are acceptable to support the use of this product for the proposed indication.

To assess the impact of excluding such sites from the efficacy analyses, results in Table 68 and Table 69 present analyses including all sites and excluding the aforementioned sites. The results were similar across the two analyses for all primary and secondary endpoints.

**Table 68. Results for the Primary and Secondary Endpoints at Week 16 With and Without Sites 423 and 435—ECZTRA-2 (FAS; Primary Analysis; Primary Estimand[1])**

| | All Sites | | Excluding Sites 423 and 435 | |
|---|---|---|---|---|
| Endpoint | TralokinumabQ2W (N=591) | Placebo (N=201) | TralokinumabQ2W (N=591) | Placebo (N=201) |
| IGA 0/1 (Primary) | 131 (22%) | 22 (11%) | 123 (21%) | 18 (9%) |
| Difference (95% CI) | 11% (6%, 16%) | | 12% (7%, 17%) | |
| P-Value | <0.001 | | <0.001 | |
| EASI-75 | 196 (33%) | 23 (11%) | 188 (33%) | 19 (10%) |
| Difference (95% CI) | 22% (16%, 27%) | | 22% (17%, 28%) | |
| P-Value | <0.001 | | <0.001 | |
| Worst Daily Pruritus NRS[2] | 144/575 (25%) | 19/200 (10%) | 141/563 (25%) | 17/192 (9%) |
| Difference (95% CI) | 16% (10%, 21%) | | 16% (11%, 21%) | |
| P-Value | <0.001 | | <0.001 | |

Source: Reviewer's analysis (same as Applicant's analysis).
[1] FAS defined as all randomized subjects who were dosed. Subjects who received rescue medication considered nonresponders; subjects with missing data at Week 16 imputed as nonresponders
[2] Reduction of Worst Daily Pruritus NRS score (weekly average) ≥4 from baseline to Week 16, among subjects with a baseline score of ≥4.
Difference, 95% CI, and p-value are based on the Cochran–Mantel–Haenszel test stratified by region and baseline IGA score.
Abbreviations: CI, confidence interval; EASI-75, at least 75% reduction in EASI score; ECZTRA, ECZema TRAlokinumab; FAS, full analysis set; IGA, Investigator's Global Assessment; NRS, numeric rating scale; Q2W, every 2 weeks

**Table 69. Results for the Primary and Secondary Endpoints at Week 16 With and Without Site 818—ECZTRA-3 (FAS; Primary Analysis; Primary Estimand[1])**

| | All Sites | | Excluding Site 818 | |
|---|---|---|---|---|
| Endpoint | Tralokinumab Q2W+TCS (N=252) | Placebo +TCS (N=126) | Tralokinumab Q2W+TCS (N=243) | Placebo +TCS (N=123) |
| IGA 0/1 (Primary) | 98 (39%) | 33 (27%) | 92 (38%) | 33 (27%) |
| Difference (95% CI) | 12% (3%, 22%) | | 11% (1%, 21%) | |
| P-Value | 0.015 | | 0.033 | |
| EASI-75 | 141 (56%) | 45 (37%) | 136 (56%) | 45 (37%) |
| Difference (95% CI) | 20% (10%, 30.6%) | | 20% (9%, 30%) | |
| P-Value | <0.001 | | <0.001 | |
| Worst Daily Pruritus NRS[2] | 113/249 (45%) | 43/126 (34%) | 111/240 (46%) | 43/123 (35%) |
| Difference (95% CI) | 11.3% (1%, 22%) | | 11.4% (1%, 22%) | |
| P-Value | 0.040 | | 0.040 | |

Source: Reviewer's analysis (same as Applicant's analysis).
[1] FAS defined as all randomized subjects who were dosed: Subjects who received rescue medication considered nonresponders; Subjects with missing data at Week 16 imputed as nonresponders.
[2] Reduction of Worst Daily Pruritus NRS score (weekly average) ≥4 from baseline to Week 16, among subjects with a baseline score of ≥4.
Difference, 95% CI, and p-value are based on the Cochran–Mantel–Haenszel test stratified by region and baseline IGA score.
Abbreviations: CI, confidence interval; EASI-75, at least 75% reduction in EASI score; ECZTRA, ECZema TRAlokinumab; FAS, full analysis set; IGA, Investigator's Global Assessment; NRS, numeric rating scale; Q2W, every 2 weeks; TCS, topical corticosteroid

# 16.1. Different Approaches for Handling Missing Data

Table 70 lists the proportion of subjects with missing data for the primary efficacy endpoint by week, treatment arm, and trial for the initial period.

**Table 70. Missing Data for the Primary Efficacy Endpoint by Week During the Initial Period—ECZTRA-1, ECZTRA-2, and ECZTRA-3 (FAS[1])**

| | ECZTRA-1 | | ECZTRA-2 | | ECZTRA-3 | |
|---|---|---|---|---|---|---|
| Week | Tralokinumab Q2W (N=601) | Placebo (N=197) | Tralokinumab Q2W (N=577) | Placebo (N=193) | Tralokinumab Q2W+TCS N=243) | Placebo +TCS (N=123) |
| Week 2 | 8 (1%) | 3 (1%) | 4 (1%) | 6 (3%) | 2 (1%) | 2 (2%) |
| Week 4 | 13 (2%) | 9 (5%) | 17 (3%) | 12 (6%) | 5 (2%) | 0 (0%) |
| Week 6 | 23 (4%) | 11 (6%) | 14 (2%) | 14 (7%) | 5 (2%) | 1 (1%) |
| Week 8 | 31 (5%) | 13 (7%) | 21 (4%) | 15 (8%) | 9 (4%) | 4 (3%) |
| Week 10 | 37 (6%) | 18 (9%) | 31 (5%) | 19 (10%) | 15 (6%) | 8 (6%) |
| Week 12 | 41 (7%) | 20 (10%) | 30 (5%) | 24 (12%) | 14 (6%) | 7 (6%) |
| Week 14 | 55 (9%) | 21 (11%)) | 39 (7%) | 22 (12%) | 17 (7%) | 8 (6%) |
| Week 16 | 40 (7%) | 15 (8%) | 24 (4%) | 16 (9%) | 11 (4%) | 3 (2%) |

Source: Statistical Reviewer's analysis; Sites 423, 435 (ECZTRA-2), and 818 (ECZTRA-3) were removed.
[1] FAS defined as all randomized subjects who were dosed.
Abbreviations: ECZTRA, ECZema TRAlokinumab; FAS, full analysis set; NRS, numeric rating scale; Q2W, every 2 weeks; TCS, topical corticosteroid

Table 71 to Table 73 present the results for the primary and secondary efficacy endpoints in all three pivotal trials by the various imputation methods for each estimand. For the tertiary ('treatment policy') estimand, the primary analysis was not conducted for the endpoint based on pruritus NRS due to unavailability of eDiary data after discontinuation of IMP. However, the corresponding planned sensitivity analysis was conducted, analyzing subjects with missing Week 16 data as nonresponders. In addition, for the primary analysis of the tertiary estimand in ECZTRA-3, the CI and p-value were not calculated for the primary endpoint of IGA 0/1 because between-imputation variance was zero. This could be due to the small amount of missing data at Week 16 and the fact that the imputation was conducted within four groups (based on treatment arm and whether the subjects had permanently discontinued treatment prior to Week 16). The results for all endpoints in consideration were similar across the primary analysis and the sensitivity analyses for each estimand.

**Table 71. Comparison of Approaches for Handling Missing Data—ECZTRA-1 (FAS*)**

| Parameter | Tralokinumab Q2W (N=601) | Placebo (N=197) | Difference (95% CI) | P-Value |
|---|---|---|---|---|
| **IGA 0/1 at Week 16** | | | | |
| Primary estimand | | | | |
| Primary analysis[1] | 95 (16%) | 14 (7%) | 9% (4%, 13%) | 0.0017 |
| Sensitivity analysis 1[2] | 95 (16%) | 14 (7%) | 9% (4%, 13%) | 0.0017 |
| Sensitivity analysis 2[3] | 96 (16%) | 15 (8%) | 8% (4%, 13%) | 0.0027 |
| Secondary estimand | | | | |
| Primary analysis[4] | 22% | 13% | 9% (2%, 16%) | 0.0100 |
| Sensitivity analysis[5] | 21% | 13% | 8% (2%, 15%) | 0.0143 |
| Tertiary estimand | | | | |
| Primary analysis[6] | 21% | 8% | 12% (7%, 17%) | <0.001 |
| Sensitivity analysis[7] | 115 (19%) | 16 (8%) | 11% (6%, 16%) | <0.001 |
| **EASI-75 at Week 16** | | | | |
| Primary estimand | | | | |
| Primary analysis[1] | 150 (25%) | 25 (13%) | 12% (7%, 18%) | <0.001 |
| Sensitivity analysis 1[2] | 148 (25%) | 24 (12%) | 12% (7%, 18%) | <0.001 |
| Sensitivity analysis 2[3] | 154 (26%) | 26 (13%) | 12% (7%, 18%) | <0.001 |
| Secondary estimand | | | | |
| Primary analysis[4] | 32% | 17% | 15% (7%, 22%) | <0.001 |
| Sensitivity analysis[5] | 30% | 17% | 13% (6%, 20%) | <0.001 |
| Tertiary estimand | | | | |
| Primary analysis[6] | 35% | 20% | 15% (9%, 22%) | <0.001 |
| Sensitivity analysis[7] | 201 (33%) | 34 (17%) | 16% (10%, 22%) | <0.001 |
| **Worst Daily Pruritus NRS at Week 16**** | | | | |
| Primary estimand | | | | |
| Primary analysis[1] | 119/594 (20%) | 20/194 (10%) | 10% (4%, 15%) | 0.002 |
| Sensitivity analysis 1[2] | 119/594 (20%) | 20/194 (10%) | 10% (4%, 15%) | 0.002 |
| Sensitivity analysis 2[3] | 128/594 (22%) | 21/194 (11%) | 11% (5%, 16%) | <0.001 |
| Secondary estimand | | | | |
| Primary analysis[4] | 29% | 17% | 13% (5%, 20%) | 0.0012 |
| Sensitivity analysis[5] | 27% | 16% | 11% (3%, 18%) | 0.0048 |
| Tertiary estimand | | | | |
| Sensitivity analysis[7] | 164/594 (28%) | 38/194 (20%) | 8% (1%, 15%) | 0.0260 |

Source: Statistical Reviewer's analysis (same as Applicant's analysis).
* FAS defined as all randomized subjects who were dosed.
** Reduction of Worst Daily Pruritus NRS score (weekly average) ≥4 from baseline to Week 16, among subjects with a baseline score of ≥4.
[1] Subjects who received rescue medication considered nonresponders. Subjects with missing data at Week 16 imputed as nonresponders.
[2] Subjects who permanently discontinued investigational medicinal product prior to Week 16 considered nonresponders.
[3] Missing data at Week 16 imputed using last observation carried forward for subjects who did not receive rescue medication and did not withdraw due to an adverse event or lack of efficacy.
[4] Data collected after permanent discontinuation of investigational medicinal product or initiation of rescue medication not included. Multiple imputation of missing values at Week 16.
[5] Placebo based imputation of missing values in active treatment group.
[6] All data used as observed at Week 16. Multiple imputation of missing values.
[7] Missing values at Week 16 imputed as nonresponders.
Difference, 95% CI, and p-value are based on the Cochran–Mantel–Haenszel test stratified by region and baseline IGA score.
Abbreviations: CI, confidence interval; EASI-75, at least 75% reduction in Eczema Area and Severity Index score; ECZTRA, ECZema TRAlokinumab; FAS, full analysis set; Investigator's Global Assessment; NRS, numeric rating scale; Q2W, every 2 weeks

**Table 72. Comparison of Approaches for Handling Missing Data—ECZTRA-2 (FAS*)**

| Parameter | Tralokinumab Q2W (N=577) | Placebo (N=193) | Difference (95% CI) | P-Value |
|---|---|---|---|---|
| **IGA 0/1 at Week 16** | | | | |
| Primary estimand | | | | |
| Primary analysis[1] | 123 (21%) | 18 (9%) | 12% (7%, 17%) | <0.001 |
| Sensitivity analysis 1[2] | 123 (21%) | 18 (9%) | 12% (7%, 17%) | <0.001 |
| Sensitivity analysis 2[3] | 123 (21%) | 18 (9%) | 12% (7%, 17%) | <0.001 |
| Secondary estimand | | | | |
| Primary analysis[4] | 26% | 18% | 7% (-1%, 16%) | 0.0959 |
| Sensitivity analysis[5] | 27% | 19% | 8% (<1%, 16%) | 0.0438 |
| Tertiary estimand | | | | |
| Primary analysis[6] | 24% | 12% | 12% (5%, 18%) | <0.001 |
| Sensitivity analysis[7] | 134 (23%) | 21 (11%) | 12% (7%, 18%) | <0.001 |
| **EASI-75 at Week 16** | | | | |
| Primary estimand | | | | |
| Primary analysis[1] | 188 (33%) | 19 (10%) | 22% (17%, 28%) | <0.001 |
| Sensitivity analysis 1[2] | 188 (33%) | 19 (10%) | 22% (17%, 28%) | <0.001 |
| Sensitivity analysis 2[3] | 188 (33%) | 19 (10%) | 22% (17%, 28%) | <0.001 |
| Secondary estimand | | | | |
| Primary analysis[4] | 38% | 14% | 23% (16%, 31%) | <0.001 |
| Sensitivity analysis[5] | 37% | 14% | 22% (15%, 29%) | <0.001 |
| Tertiary estimand | | | | |
| Primary analysis[6] | 38.9% | 18% | 21% (14%, 28%) | <0.001 |
| Sensitivity analysis[7] | 216 (37%) | 29 (15%) | 22% (16%, 29%) | <0.001 |
| **Worst Daily Pruritus NRS at Week 16**** | | | | |
| Primary estimand | | | | |
| Primary analysis[1] | 141/563 (25%) | 17/192 (9%) | 16.3% (11%, 21%) | <0.001 |
| Sensitivity analysis 1[2] | 141/563 (25%) | 17/192 (9%) | 16.3% (11%, 21%) | <0.001 |
| Sensitivity analysis 2[3] | 152/563 (27%) | 17/192 (9%) | 17.9 (13%, 23%) | <0.001 |
| Secondary estimand | | | | |
| Primary analysis[4] | 33% | 15% | 18% (10%, 25%) | <0.001 |
| Sensitivity analysis[5] | 31% | 15% | 16% (8%, 23%) | <0.001 |
| Tertiary estimand | | | | |
| Sensitivity analysis[7] | 167/563 (30%) | 37/192 (19%) | 10% (4%, 17%) | 0.0054 |

Source: Statistical Reviewer's analysis; Sites 423 and 435 were removed.
* FAS defined as all randomized subjects who were dosed.
** Reduction of Worst Daily Pruritus NRS score (weekly average) ≥4 from baseline to Week 16, among subjects with a baseline score of ≥4.
[1] Subjects who received rescue medication considered nonresponders. Subjects with missing data at Week 16 imputed as nonresponders.
[2] Subjects who permanently discontinued investigational medicinal product prior to Week 16 considered nonresponders.
[3] Missing data at Week 16 imputed using last observation carried forward for subjects who did not receive rescue medication and did not withdraw due to an AE or lack of efficacy.
[4] Data collected after permanent discontinuation of investigational medicinal product or initiation of rescue medication not included. Multiple imputation of missing values at Week 16.
[5] Placebo based imputation of missing values in active treatment group.
[6] All data used as observed at Week 16. Multiple imputation of missing values.
[7] Missing values at Week 16 imputed as nonresponders.
Difference, 95% CI, and p-value are based on the Cochran–Mantel–Haenszel test stratified by region and baseline IGA score.
Abbreviations: CI, confidence interval; EASI-75, at least 75% reduction in Eczema Area and Severity Index score; ECZTRA, ECZema TRAlokinumab; FAS, full analysis set; Investigator's Global Assessment; NRS, numeric rating scale; Q2W, every 2 weeks

**Table 73. Comparison of Approaches for Handling Missing Data—ECZTRA-3 (FAS*)**

| Parameter | Tralokinumab Q2W+TCS (N=243) | Placebo +TCS (N=123) | Difference (95% CI) | P-Value |
|---|---|---|---|---|
| **IGA 0/1 at Week 16** | | | | |
| Primary estimand | | | | |
| Primary analysis[1] | 92 (38%) | 33 (27%) | 11% (1%, 21%) | 0.0327 |
| Sensitivity analysis 1[2] | 92 (38%) | 33 (27%) | 11% (1%, 21%) | 0.0327 |
| Sensitivity analysis 2[3] | 93 (38%) | 33 (27%) | 12% (2%, 21%) | 0.0265 |
| Secondary estimand | | | | |
| Primary analysis[4] | 41% | 29% | 11% (11%, 22%) | 0.0308 |
| Sensitivity analysis[5] | 41% | 29% | 12% (11%, 22%) | 0.0278 |
| Tertiary estimand | | | | |
| Primary analysis[6] | 38% | 27% | 11% (-, -) | - |
| Sensitivity analysis[7] | 92 (38%) | 33 (27%) | 11% (1%, 21%) | 0.0327 |
| **EASI-75 at Week 16** | | | | |
| Primary estimand | | | | |
| Primary analysis[1] | 136 (56%) | 45 (37%) | 20% (9%, 30%) | <0.001 |
| Sensitivity analysis 1[2] | 135 (56%) | 44 (36%) | 20% (9%, 30%) | <0.001 |
| Sensitivity analysis 2[3] | 138 (57%) | 46 (37%) | 20% (9%, 30%) | <0.001 |
| Secondary estimand | | | | |
| Primary analysis[4] | 59% | 38% | 21% (10%, 32%) | <0.001 |
| Sensitivity analysis[5] | 58% | 38% | 21% (10%, 32%) | <0.001 |
| Tertiary estimand | | | | |
| Primary analysis[6] | 57% | 37% | 20% (10%, 31%) | <0.001 |
| Sensitivity analysis[7] | 136 (56%) | 45 (37%) | 20% (9%, 30%) | <0.001 |
| **Worst Daily Pruritus NRS at Week 16**** | | | | |
| Primary estimand | | | | |
| Primary analysis[1] | 111/240 (46%) | 43/123 (35%) | 11% (1%, 22%) | 0.0390 |
| Sensitivity analysis 1[2] | 111/240 (46%) | 43/123 (35%) | 11% (1%, 22%) | 0.0390 |
| Sensitivity analysis 2[3] | 120/240 (50%) | 46/123 (37%) | 13% (2%, 24%) | 0.0206 |
| Secondary estimand | | | | |
| Primary analysis[4] | 53% | 38% | 14% (3%, 25%) | 0.0165 |
| Sensitivity analysis[5] | 52% | 39% | 12% (1%, 23%) | 0.0285 |
| Tertiary estimand | | | | |
| Sensitivity analysis[7] | 113/240 (47%) | 46/123 (37%) | 9.8% (-1%, 20%) | 0.0767 |

Source: Statistical Reviewer's analysis; Site 818 was removed.
* FAS defined as all randomized subjects who were dosed.
** Reduction of Worst Daily Pruritus NRS score (weekly average) ≥4 from baseline to Week 16, among subjects with a baseline score of ≥4.
[1] Subjects who received rescue medication considered nonresponders. Subjects with missing data at Week 16 imputed as nonresponders.
[2] Subjects who permanently discontinued investigational medicinal product prior to Week 16 considered nonresponders.
[3] Missing data at Week 16 imputed using last observation carried forward for subjects who did not receive rescue medication and did not withdraw due to an adverse event or lack of efficacy.
[4] Data collected after permanent discontinuation of investigational medicinal product or initiation of rescue medication not included. Multiple imputation of missing values at Week 16.
[5] Placebo based imputation of missing values in active treatment group.
[6] All data used as observed at Week 16. Multiple imputation of missing values.
[7] Missing values at Week 16 imputed as nonresponders.
Difference, 95% CI, and p-value are based on the Cochran–Mantel–Haenszel test stratified by region and baseline IGA score.
Abbreviations: CI, confidence interval; EASI-75, at least 75% reduction in Eczema Area and Severity Index score; ECZTRA, ECZema TRAlokinumab; FAS, full analysis set; Investigator's Global Assessment; NRS, numeric rating scale; Q2W, every 2 weeks; TCS, topical corticosteroids

**IGA 0/1 at Week 16**

In ECZTRA-1, the difference in response rates between tralokinumab and placebo for the analyses of the secondary estimand (hypothetical) was similar to the treatment difference for the primary estimand (composite). However, the response rates were higher in both treatment arms. The difference in response rates was larger for analyses of the tertiary estimand (treatment policy) compared to the treatment difference obtained for the primary (composite) and secondary (hypothetical) estimands.

In ECZTRA-2, the difference in response rates between tralokinumab and placebo was lower for the analyses of the hypothetical estimand, leading to nonsignificant results for the primary analysis of this estimand (p=0.096), compared to the treatment difference for the primary estimand. This was mainly driven by a higher response rate in the placebo arm when assuming missing at random for subjects who received rescue medication or discontinued the IMP. The treatment difference could be further penalized by the higher use of rescue medication in the placebo arm (Table 14). The treatment difference obtained for the tertiary estimand was similar to that obtained for the primary estimand.

In ECZTRA-3, within each treatment arm, similar response rates were observed for the analyses of all three estimands, with slightly higher response rates for the analyses of the secondary estimand.

**EASI-75 at Week 16**

In ECZTRA-1, as seen for IGA 0/1, the difference in response rates for EASI-75 at Week 16 between tralokinumab and placebo was higher based on the analyses of the secondary estimand compared to the treatment difference obtained for the primary estimand. In analyses of the tertiary estimand, the treatment difference was slightly larger compared to that obtained for the primary and secondary estimands, with higher response rates in both treatment arms.

In ECZTRA-2, the difference in response rates between tralokinumab and placebo was similar across the analyses of the three estimands, with slightly higher response rates in both treatments arms for the analyses of the secondary and tertiary estimands.

In ECZTRA-3, similar to IGA 0/1, within each treatment arm, similar results for the EASI-75 were observed for the analyses of all three estimands, with slightly higher response rates for the analyses of the secondary estimand.

**Worst Daily Pruritus NRS at Week 16**

In ECZTRA-1, as seen for IGA 0/1 and EASI-75, the difference in response rates with regards to ≥4-point reduction of Worst Daily Pruritus NRS from baseline to Week 16 between tralokinumab and placebo was higher based on the analyses of the secondary estimand compared to the treatment difference obtained for the primary estimand, with higher response rates in both treatment arms. Unlike the other two endpoints in consideration (i.e., IGA 0/1 and EASI-75), the treatment difference was lower based on the analysis for the tertiary estimand compared to the analyses of the primary and secondary estimands.

In ECZTRA-2, the difference in response rates with regards to ≥4-point reduction of Worst Daily Pruritus NRS from baseline to Week 16 was similar across the analyses for the primary and

secondary estimands. The treatment difference based on the analysis of the tertiary estimand was lower based on the analysis for the tertiary estimand compared to the analyses of the primary and secondary estimands.

In ECZTRA-3, the difference in response rates with regards to ≥4-point reduction of Worst Daily Pruritus NRS from baseline to Week 16 was higher based on the analyses of the secondary estimand compared to the treatment difference obtained for the primary estimand, with higher response rates in both treatment arms.

## 16.2. Additional Analyses—EASI-90

The results for the endpoint of EASI-90 at Week 16, defined as at least 90% reduction from baseline, are summarized in Table 74 and Table 75. The results for such endpoint are viewed as exploratory for this review.

**Table 74. Results for EASI-90 at Week 16—ECZTRA-1 and ECZTRA-2 (FAS; Primary Analysis; Primary Estimand[1])**

| | ECZTRA-1 | | ECZTRA-2 | |
|---|---|---|---|---|
| Endpoint | Tralokinumab Q2W (N=601) | Placebo (N=197) | Tralokinumab Q2W (N=577) | Placebo (N=193) |
| EASI-90 | 87 (14%) | 8 (4%) | 107 (18%) | 10 (5%) |

Source: Statistical Reviewer's analysis (same as Applicant's analysis except Sites 423 and 435 are excluded Site 818 in the above table).
[1] FAS defined as all randomized subjects who were dosed. Subjects who received rescue medication considered nonresponders; Subjects with missing data at Week 16 imputed as nonresponders.
Abbreviations: EASI-90, at least 90% reduction in Eczema Area and Severity Index score; ECZTRA, ECZema TRAlokinumab; FAS, full analysis set; Q2W, every 2 weeks

**Table 75. Results for EASI-90 at Week 16 at Week 16—ECZTRA-3 (FAS; Primary Analysis; Primary Estimand[1])**

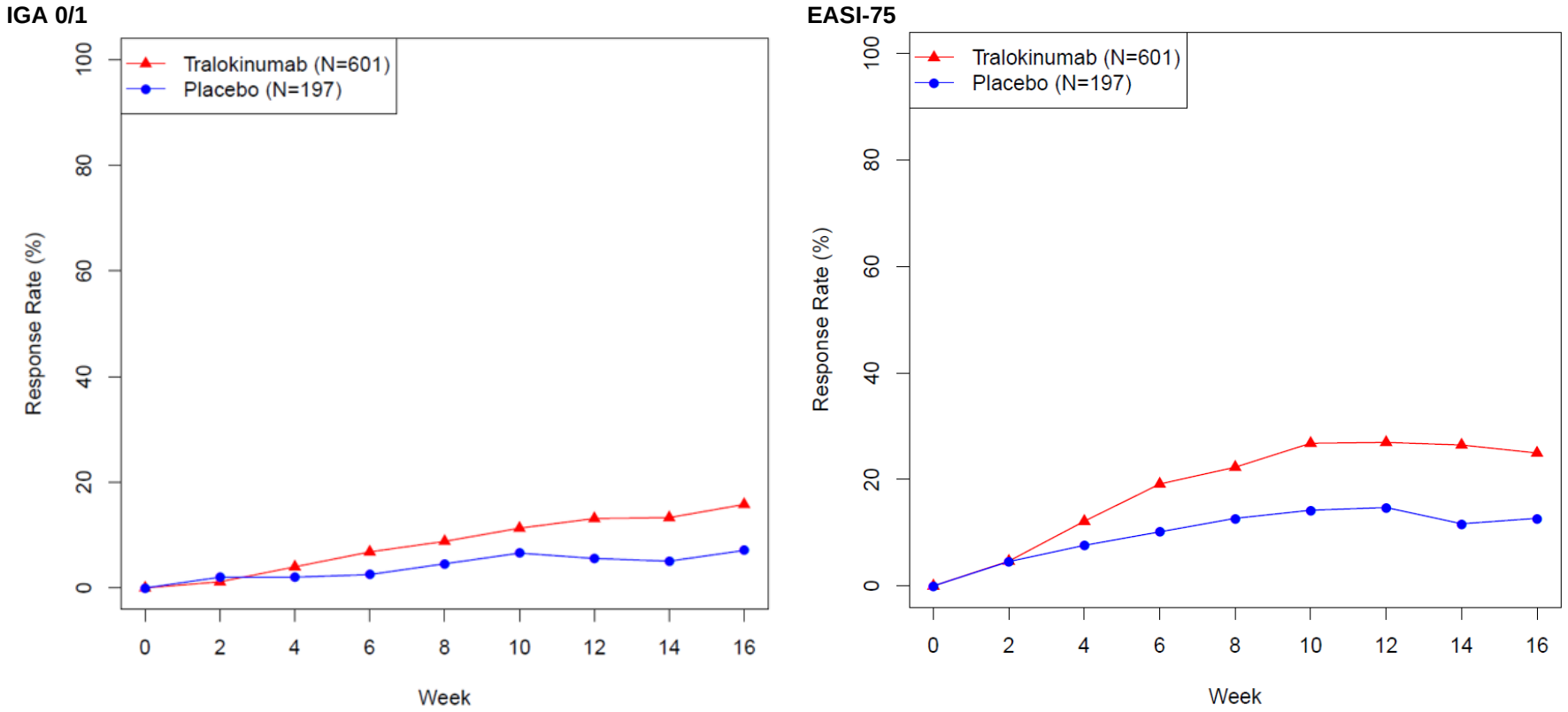
| Endpoint | Tralokinumab Q2W+TCS (N=243) | Placebo +TCS (N=123) |
|---|---|---|
| EASI-90 | 82 (34%) | 27 (22%) |

Source: Statistical Reviewer's analysis (same as Applicant's analysis except site 818 is excluded in the above table).
[1] FAS defined as all randomized subjects who were dosed. Subjects who received rescue medication considered nonresponders; subjects with missing data at Week 16 imputed as nonresponders.
Abbreviations: EASI-90, at least 90% reduction in Eczema Area and Severity Index score; ECZTRA, ECZema TRAlokinumab; FAS, full analysis set; Q2W, every 2 weeks; TCS, topical corticosteroid

## 16.3. Efficacy Over Time During the Initial Treatment Period

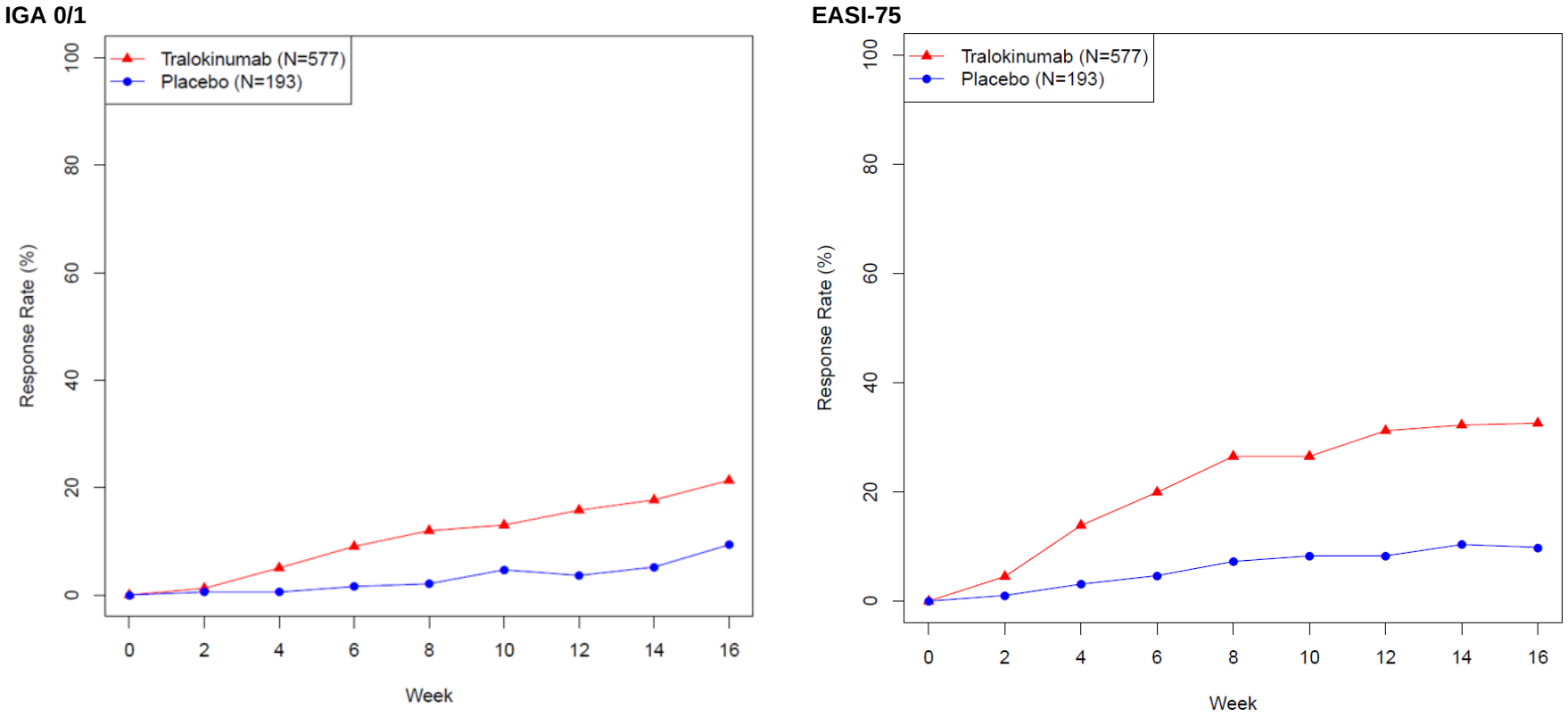
For the initial treatment period, subjects were evaluated for IGA and EASI scores at baseline and Weeks 2, 4, 6, 8, 10, 12, and 16. Figure 42 to Figure 44 show the IGA (IGA of 0/1) and EASI-75 response rates over time.

**Figure 42. Efficacy Over Time for the Initial Treatment Period—Trial ECZTRA-1 (FAS; NRI[1])**



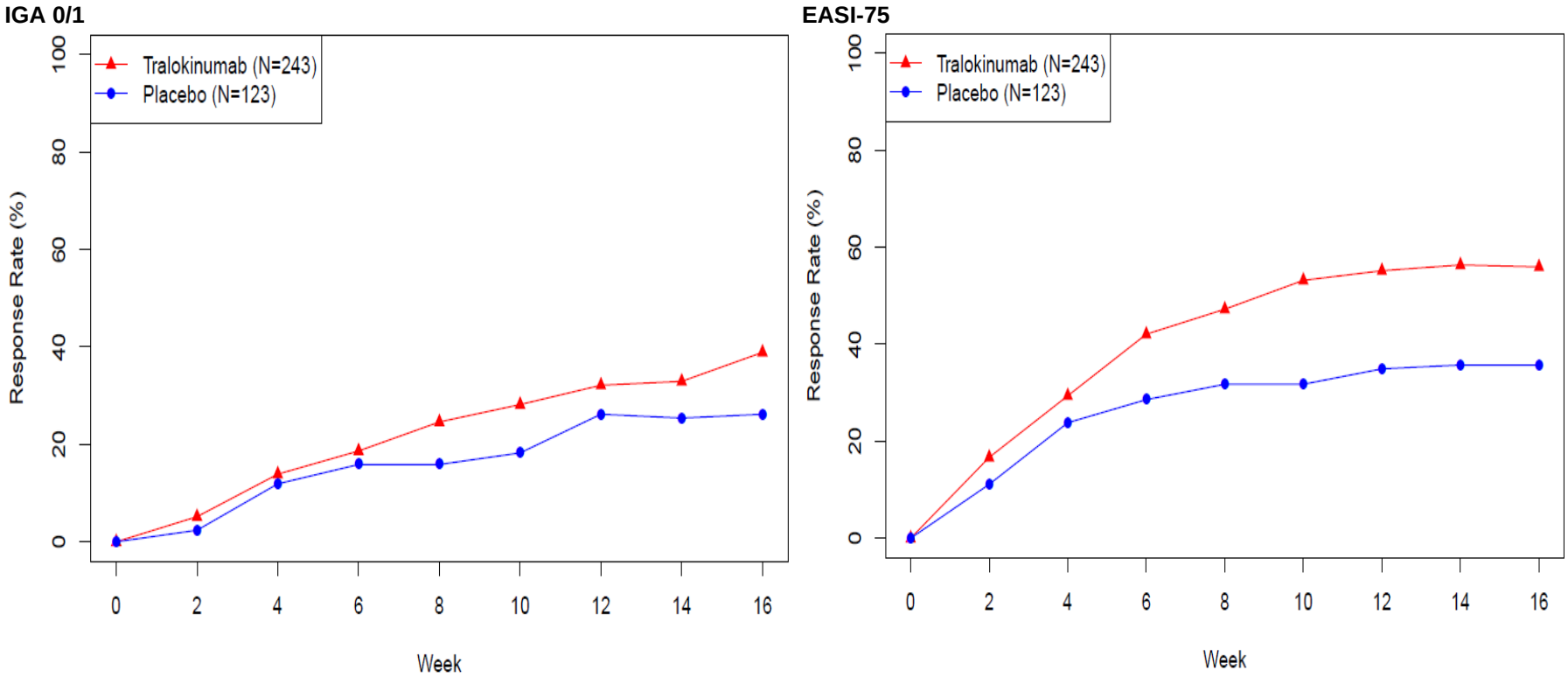

Source: Statistical Reviewer's analysis.
[1] FAS defined as all randomized subjects who were dosed: Subjects who received rescue medication considered nonresponders; subjects with missing data at Week 16 imputed as nonresponders.
Abbreviations: EASI-75, at least 75% reduction in Eczema Area and Severity Index score; ECZTRA, ECZema TRAlokinumab; FAS, full analysis set; Investigator's Global Assessment; NRI, nonresponder imputation

**Figure 43. Efficacy Over Time for the Initial Treatment Period—ECZTRA-2 (FAS; NRI[1])**




Source: Statistical Reviewer's analysis; Sites 423 and 435 were removed.
[1] FAS defined as all randomized subjects who were dosed: Subjects who received rescue medication considered nonresponders. Subjects with missing data at Week 16 imputed as nonresponders.
Abbreviations: EASI-75, at least 75% reduction in Eczema Area and Severity Index score; ECZTRA, ECZema TRAlokinumab; FAS, full analysis set; Investigator's Global Assessment; NRI, nonresponder imputation

**Figure 44. Efficacy Over Time for the Initial Treatment Period—Trial ECZTRA-3 (FAS; NRI[1])**




Source: Statistical Reviewer's analysis; Site 818 was removed.
[1] FAS defined as all randomized subjects who were dosed: Subjects who received rescue medication considered nonresponders. Subjects with missing data at Week 16 imputed as nonresponders.
Abbreviations: EASI-75, at least 75% reduction in Eczema Area and Severity Index score; ECZTRA, ECZema TRAlokinumab; FAS, full analysis set; Investigator's Global Assessment; NRI, nonresponder imputation

# 16.4. Disposition During the Maintenance Treatment Period

In ECZTRA-1, among the 601 randomized and dosed subjects in the tralokinumab Q2W arm during the initial treatment period, 185 subjects were Week 16 tralokinumab responders and were rerandomized (2:2:1) to the maintenance treatment period. Among these 185 subjects, 6 were not dosed, 62 were transferred to the open-label period, and 14 subjects permanently discontinued the IMP without entering the open-label period. Therefore, the maintenance analysis set consisted of 179 subjects.

In ECZTRA-2, among the 577 randomized and dosed subjects in the tralokinumab Q2W arm during the initial treatment period, 219 were rerandomized (2:2:1) to the maintenance treatment period. Among these 219 subjects, 1 was not dosed (transferred to open-label), 81 were transferred to the open-label period, and 20 subjects did not enter the open-label period and permanently discontinued the IMP. Therefore, the maintenance analysis set consisted of 218 subjects. For the disposition of subjects during the maintenance period in the monotherapy trials see Table 76.

In ECZTRA-3, among the 243 randomized and dosed subjects in the tralokinumab Q2W+TCS arm during the initial treatment period, 131 subjects were rerandomized (and dosed) in the continuation treatment period (continuation treatment analysis set). For the disposition of subjects during the continuation treatment period, refer to Table 77. It is noted that one subject in the tralokinumab Q2W+TCS arm and three subjects in the tralokinumab Q4W+TCS arm were rerandomized in error; all four subjects were Week 16 nonresponders.

**Table 76. Disposition of Subjects During the Maintenance Period—ECZTRA-1 and ECZTRA-2**

| | ECZTRA-1 | | | ECZTRA-2 | | |
|---|---|---|---|---|---|---|
| Parameter | Tralokinumab Q2W | Tralokinumab Q4W | Placebo | Tralokinumab Q2W | Tralokinumab Q4W | Placebo |
| Assigned maintenance treatment | 71 | 78 | 36 | 90 | 85 | 44 |
| Not dosed | 3 | 2 | 1 | 0 | 1 | 0 |
| Maintenance analysis set | 68 | 76 | 35 | 90 | 84 | 44 |
| Transferred to open-label | 23 | 19 | 10 | 29 | 27 | 26 |
| Permanently discontinued[1] | 4 | 6 | 4 | 8 | 8 | 4 |

Source: Statistical Reviewer's analysis; Sites 423 and 435 from ECZTRA-2 were removed.
[1] Subjects who permanently discontinued without entering the open-label period.
The table lists only subjects who were randomized in the tralokinumab Q2W arm during the initial treatment period.
Abbreviations: ECZTRA, ECZema TRAlokinumab; Q2W, every 2 weeks; Q4W, every 4 weeks

**Table 77. Disposition of Subjects During the Continuation Treatment Period—ECZTRA-3**

| Parameter | Tralokinumab Q2W+TCS | Tralokinumab Q4W+TCS |
|---|---|---|
| Assigned to maintenance treatment | 65 | 66 |
| Not dosed | 0 | 0 |
| Continuation treatment analysis set | 65 | 66 |
| Permanently discontinued | 1 | 3 |

Source: Statistical Reviewer's analysis; Site 818 was removed.
The analysis includes only Week 16 responders.
Abbreviations: ECZTRA, ECZema TRAlokinumab; Q2W, every 2 weeks; Q4W, every 4 weeks; TCS, topical corticosteroids

# 16.5. Efficacy Over Time During the Maintenance Treatment Period

## Monotherapy Trials (ECZTRA-1 and ECZTRA-2)

Figure 45 presents the IGA response rates during the maintenance period (Weeks 16 to 52) for the rerandomized subjects who were IGA 0/1 responders at Week 16 in the monotherapy trials.

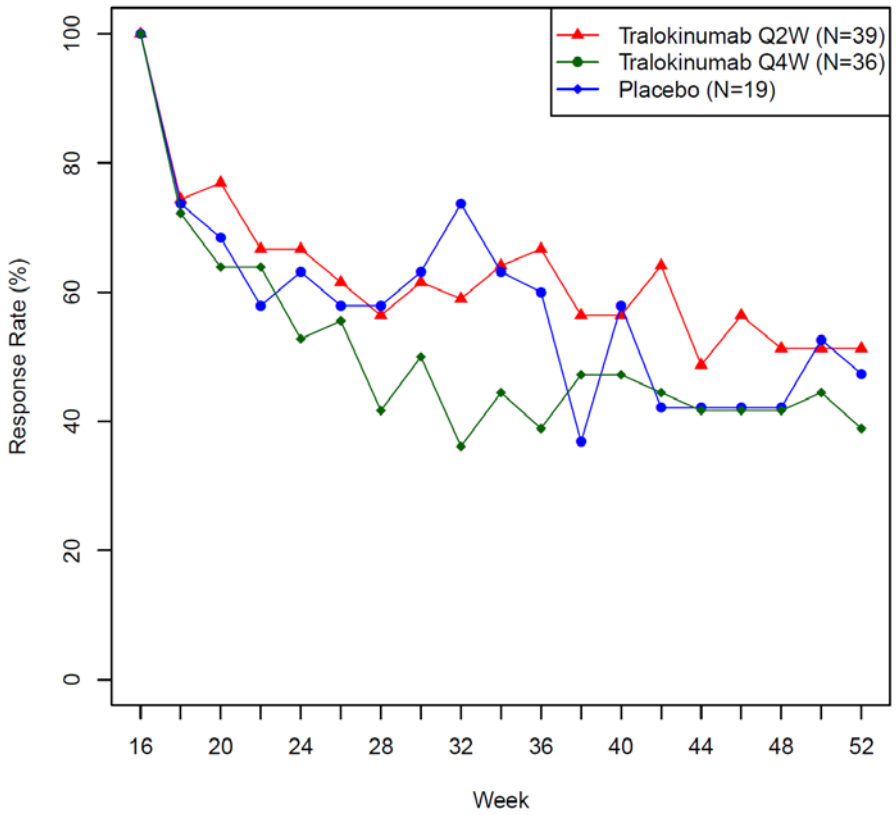
Figure 46 presents the EASI-75 response rates during the maintenance period for the rerandomized subjects who were EASI-75 responders at Week 16 in the monotherapy trials.

Figure 47 presents the IGA response rates during the continuation treatment period (Weeks 16 to 32) for the rerandomized subjects who were IGA 0/1 responders at Week 16 in ECZTRA-3.

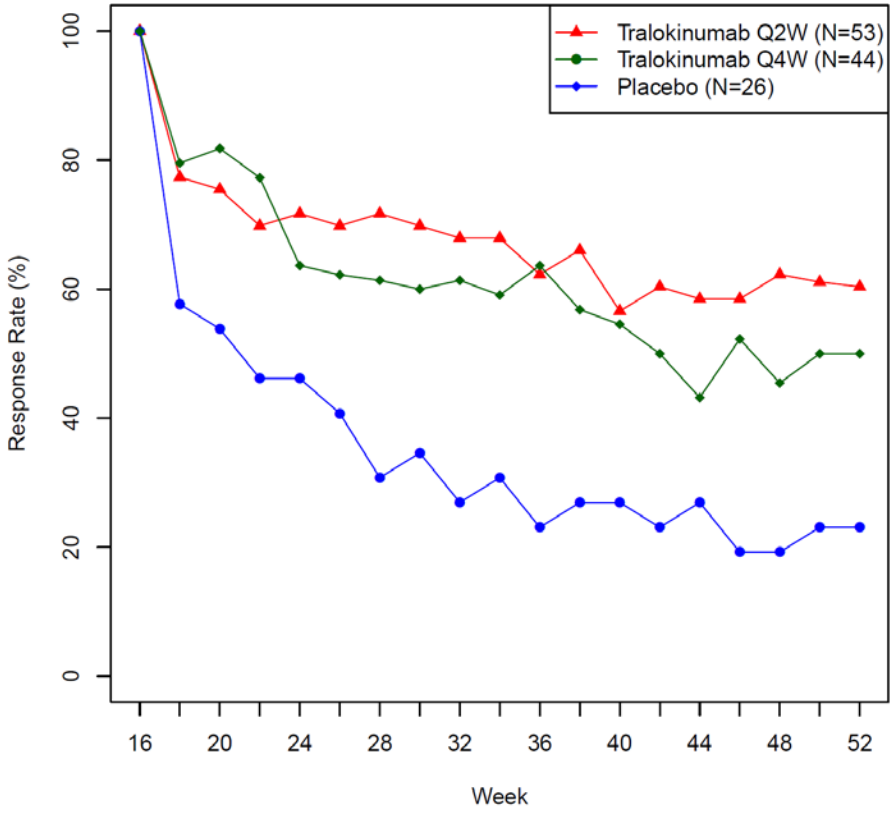
Figure 48 presents the EASI-75 response rates during the continuation treatment period (Weeks 16 to 32) for the rerandomized subjects who were EASI-75 responders at Week 16 in ECZTRA-3.

**Figure 45. IGA Success (IGA 0 or 1) During the Maintenance Period for ECZTRA-1 and ECZTRA-2 (MAS; NRI[1])**

**ECZTRA-1**



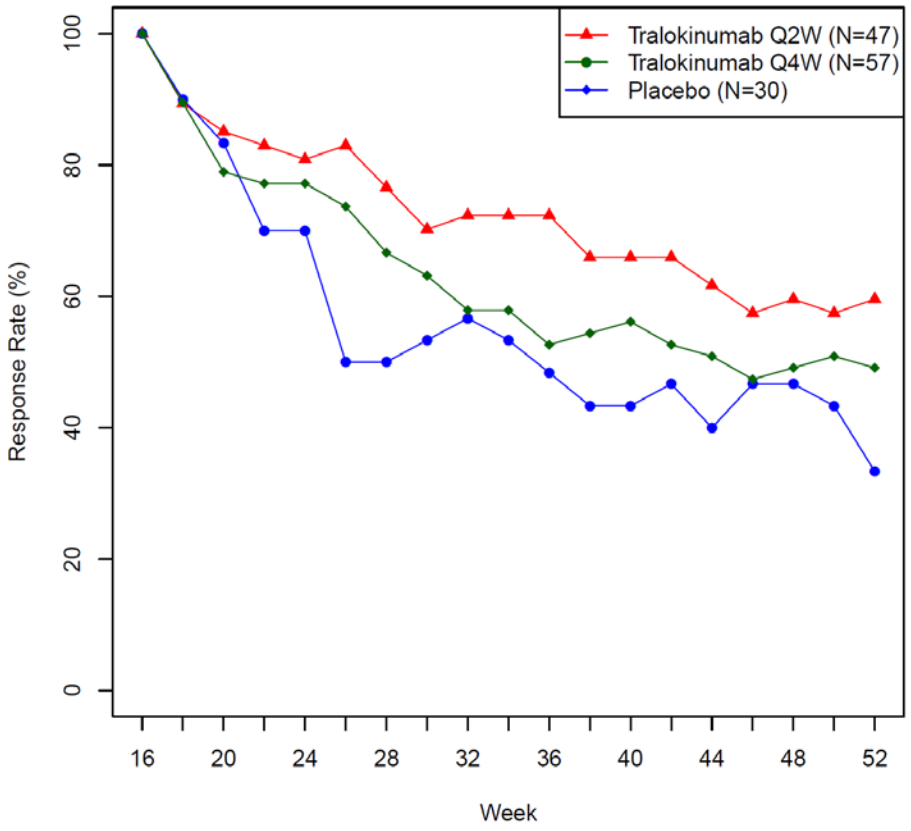

**ECZTRA-2**



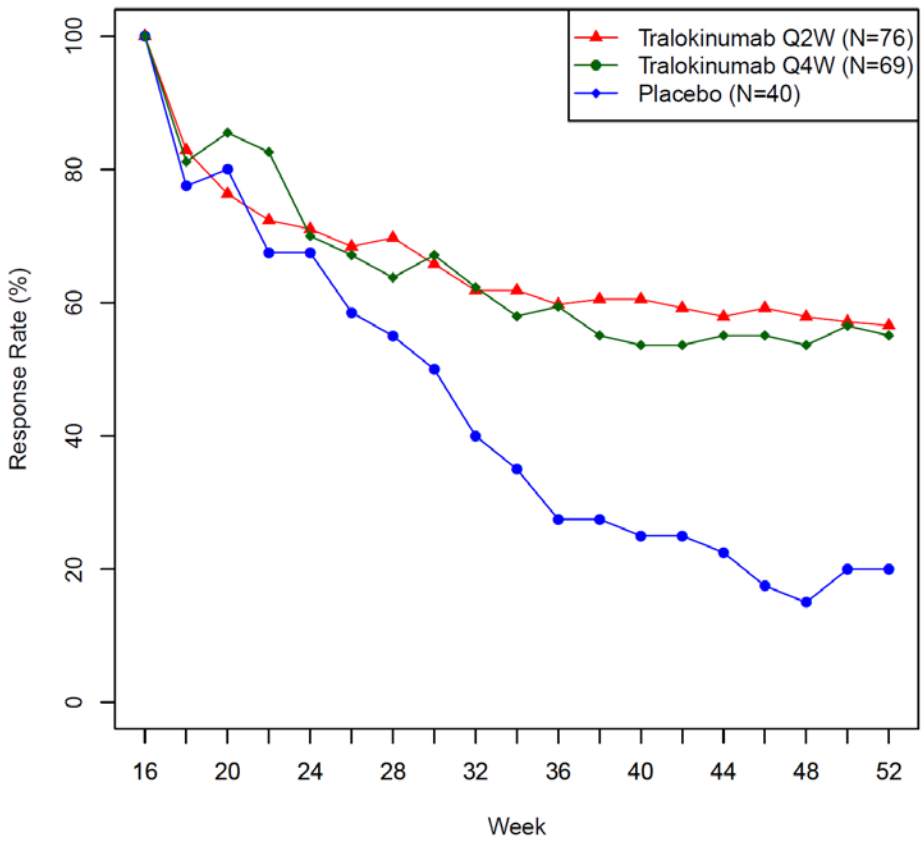

Source: Statistical Reviewer's analysis; Sites 423 and 435 from ECZTRA-2 were removed.
[1] MAS defined as all subjects who received tralokinumab in the initial treatment period and who were rerandomized to maintenance treatment; subjects who were not exposed to maintenance treatment were excluded. Subjects who received rescue medication or were transferred to open-label treatment were considered nonresponders. Missing data at Week 52 were imputed using the NRI method.
Abbreviations: ECZTRA, ECZema TRAlokinumab; IGA, Investigator's Global Assessment; MAS, maintenance analysis set; NRI, nonresponder imputation; Q2W, every 2 weeks; Q4W, every 4 weeks

**Figure 46. EASI-75 During the Maintenance Period for Trials ECZTRA-1 and ECZTRA-2 (MAS; NRI[1])**

**ECZTRA-1**

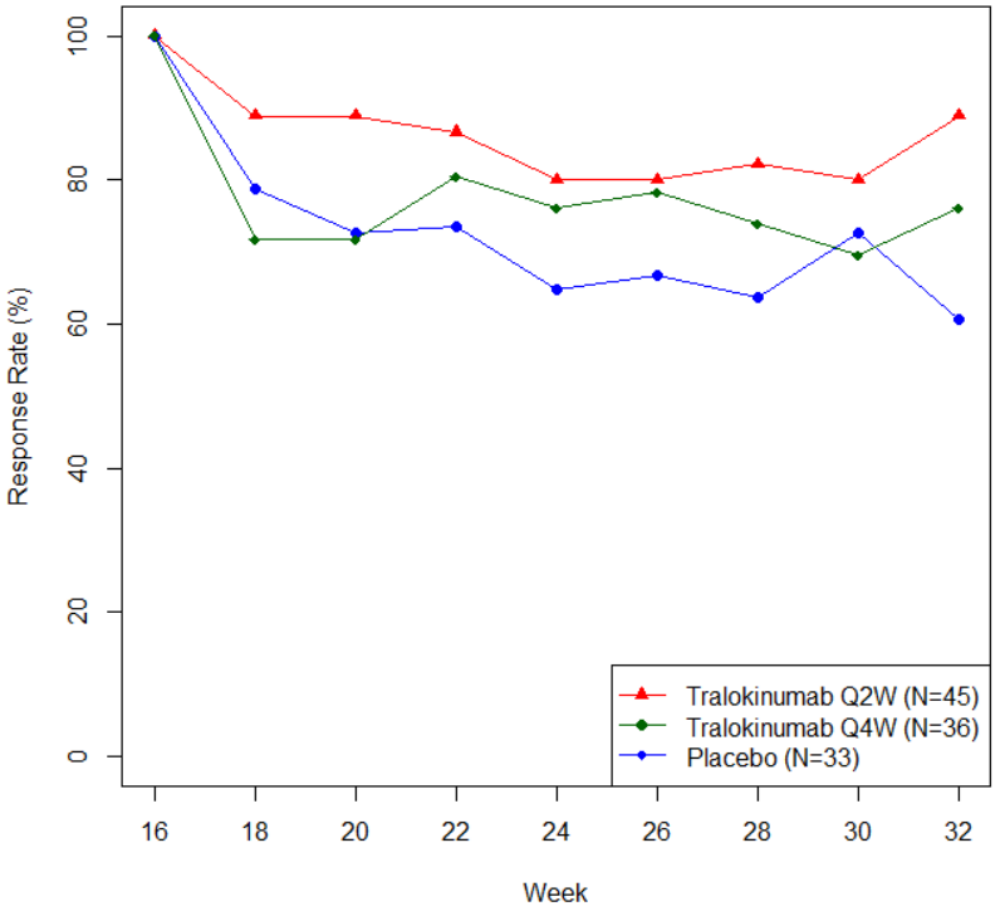



**ECZTRA-2**



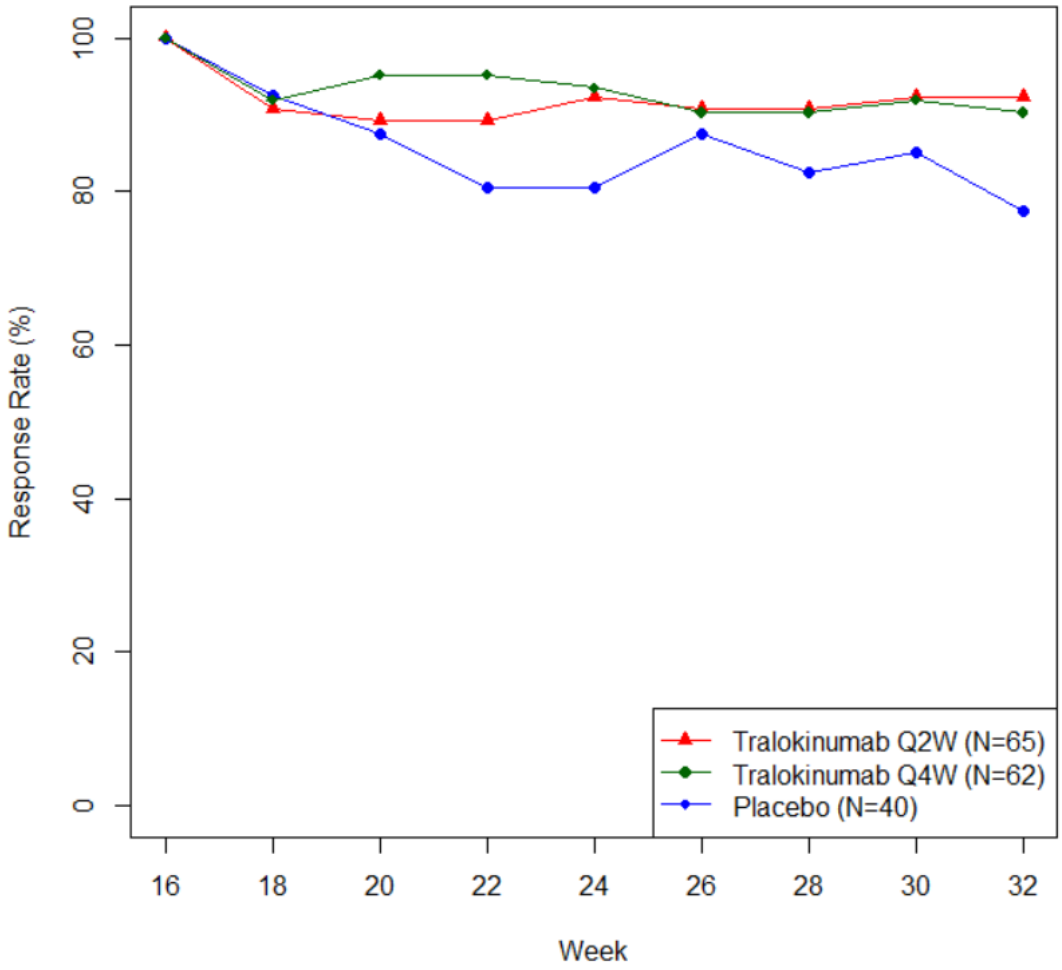

Source: Statistical Reviewer's analysis; Sites 423 and 435 from ECZTRA-2 were removed.
[1] MAS defined as all subjects who received tralokinumab in the initial treatment period and who were rerandomized to maintenance treatment; subjects who were not exposed to maintenance treatment were excluded. Subjects who received rescue medication or were transferred to open-label treatment were considered nonresponders. Subjects with missing data were imputed by the NRI method.
The analysis includes only Week 16 EASI-75 responders.
Abbreviations: EASI-75, at least 75% reduction in Eczema Area and Severity Index score; ECZTRA, ECZema TRAlokinumab; MAS, maintenance analysis set; NRI, nonresponder imputation; Q2W, every 2 weeks; Q4W, every 4 weeks

**Figure 47. IGA Success (IGA 0 or 1) During the Continuation Treatment Period for ECZTRA-3 (Continuation Treatment Analysis Set; NRI[1])**




Source: Statistical Reviewer's analysis; Site 818 was removed.
[1] Continuation treatment analysis set was defined as all randomized subjects who did not withdraw from the trial before or at the Week 16 visit and who were exposed to at least one dose of investigational medicinal product in the continuation treatment period. Subjects who received rescue medication or were transferred to open-label treatment were considered nonresponders. Missing data at Week 32 were imputed using the NRI method.
Abbreviations: ECZTRA, ECZema TRAlokinumab; Investigator's Global Assessment; MAS, maintenance analysis set; NRI, nonresponder imputation; Q2W, every 2 weeks; Q4W, every 4 weeks

**Figure 48. EASI-75 During the Continuation Treatment Period for ECZTRA-3 (Continuation Treatment Analysis Set; NRI[1])**




Source: Statistical Reviewer's analysis; Site 818 was removed.
[1] Continuation treatment analysis set was defined as all randomized subjects who did not withdraw from the trial before or at the Week 16 visit and who were exposed to at least one dose of investigational medicinal product in the continuation treatment period. Subjects who received rescue medication or were transferred to open-label treatment were considered nonresponders. Missing data at Week 32 were imputed using the NRI method.
Abbreviations: EASI-75, at least 75% reduction in Eczema Area and Severity Index score; ECZTRA, ECZema TRAlokinumab; MAS, maintenance analysis set; NRI, nonresponder imputation; Q2W, every 2 weeks; Q4W, every 4 weeks

# 16.6. Findings in Special/Subgroup Populations

**Table 78. IGA 0/1 Response at Week 16 by Age, Sex, Race, Weight, Baseline IGA Score, and Prior Use of Immunosuppressants—ECZTRA-1 (FAS; Primary Analysis; Primary Estimand[1])**

| Subgroup (n[Tral], n[P]) | Tralokinumab Q2W (N=601) | Placebo (N=197) | Difference | 95% CI |
|---|---|---|---|---|
| Age (years) | | | | |
| 18-64 (572, 183) | 16% | 8% | 8% | (3%, 13%) |
| ≥65 (29, 14) | 17% | 0% | 17% | (4%, 31%) |
| Sex | | | | |
| Male (350, 122) | 13% | 7% | 6.6% | (1%, 12%) |
| Female (251, 75) | 20% | 8% | 11.6% | (4%, 20%) |
| Race | | | | |
| White (424, 137) | 18% | 6% | 12.6% | (7%, 18%) |
| Non-white (177, 60) | 10% | 10% | <0% | (-9%, 8%) |
| Weight | | | | |
| <70 kg (252, 77) | 17% | 5% | 12% | (5%, 19%) |
| 70-100 kg (286, 107) | 15% | 7% | 7% | (1%, 14%) |
| >100 kg (63, 13) | 14% | 15% | -1% | (-22%, 20%) |
| Baseline IGA score | | | | |
| Moderate (296, 95) | 24% | 10% | 14% | (6%, 2%) |
| Severe (305, 102) | 8% | 4% | 4% | (-1%, 9%) |
| Prior use of immunosuppressants[2] | | | | |
| Yes (254, 74) | 10% | 3% | 7% | (2%, 12%) |
| No (339, 122) | 20% | 10% | 10% | (3%, 17%) |
| Overall | 16% | 7% | 9% | (4%, 13%) |

Source: Statistical Reviewer's analysis
[1] FAS defined as all randomized subjects who were dosed. Subjects who received rescue medication considered nonresponders; subjects with missing data at Week 16 imputed as nonresponders.
[2] Nine subjects (eight in the tralokinumab arm and one in the placebo arm) had unknown prior use of immunosuppressants.
Abbreviations: CI, confidence interval; ECZTRA, ECZema TRAlokinumab; FAS, full analysis set; IGA, Investigator's Global Assessment; Q2W, every 2 weeks

**Table 79. EASI-75 Response at Week 16 by Age, Sex, Race, Weight, Baseline IGA Score, and Prior Use of Immunosuppressants—ECZTRA-1 (FAS; Primary Analysis; Primary Estimand[1])**

| Subgroup (n[Tral], n[P]) | Tralokinumab Q2W (N=601) | Placebo (N=197) | Difference | 95% CI |
|---|---|---|---|---|
| Age (years) | | | | |
| 18-64 (572, 183) | 25% | 14% | 11% | (5%, 17%) |
| ≥65 (29, 14) | 31% | 0% | 31% | (14%, 48%) |
| Sex | | | | |
| Male (350, 122) | 21% | 11% | 9% | (2%, 16%) |
| Female (251, 75) | 31% | 15% | 16% | (7%, 26%) |
| Race | | | | |
| White (424, 137) | 25% | 8% | 17% | (11%, 23%) |
| Non-white (177, 60) | 25% | 23% | 2% | (-10%, 15%) |
| Weight | | | | |
| <70 kg (252, 77) | 27% | 12% | 15% | (6%, 24%) |
| 70-100 kg (286, 107) | 23% | 10% | 13% | (5%, 20%) |
| >100 kg (63, 13) | 25% | 38% | -13% | (-42%, 15%) |
| Baseline IGA | | | | |
| Moderate (296, 95) | 33% | 15% | 18% | (9%, 27%) |
| Severe (305, 102) | 17% | 11% | 6% | (-1%, 14%) |
| Prior use of immunosuppressants[2] | | | | |
| Yes (254, 74) | 16% | 8% | 8% | (<0%, 15%) |
| No (339, 122) | 31% | 16% | 16% | (8%, 24%) |
| Overall | 25% | 13% | 12% | (6%, 18%) |

Source: Statistical Reviewer's analysis.
[1] FAS defined as all randomized subjects who were dosed. Subjects who received rescue medication considered nonresponders; subjects with missing data at Week 16 imputed as nonresponders.
[2] Nine subjects (eight in the tralokinumab arm and one in the placebo arm) had unknown prior use of immunosuppressants.
Abbreviations: CI, confidence interval; EASI-75, at least 75% reduction in Eczema Area and Severity Index score; ECZTRA, ECZema TRAlokinumab; FAS, full analysis set; IGA, Investigator's Global Assessment; Q2W, every 2 weeks

**Table 80. IGA 0/1 Response at Week 16 by Age, Sex, Race, Weight, Baseline IGA Score, and Prior Use of Immunosuppressants—ECZTRA-2 (FAS; Primary Analysis; Primary Estimand[1])**

| Subgroup (n[Tral], n[P]) | Tralokinumab Q2W (N=591) | Placebo (N=201) | Difference | 95% CI |
|---|---|---|---|---|
| Age (years) | | | | |
| 18-64 (548, 186) | 21% | 10% | 12% | (6%, 17%) |
| ≥65 (29, 7) | 17% | 0% | 17% | (4%, 31%) |
| Sex | | | | |
| Male (347, 108) | 20% | 10% | 9% | (2%, 17%) |
| Female (230, 85) | 24% | 8% | 16% | (8%, 24%) |
| Race | | | | |
| White (370, 123) | 24% | 10% | 14% | (7%, 21%) |
| Non-white (207, 70) | 17% | 9% | 8% | (<1%, 17%) |
| Weight | | | | |
| <70 kg (228, 75) | 25% | 8% | 17% | (8%, 25%) |
| 70-100 kg (294, 106) | 20% | 11% | 8% | (1%, 16%) |
| >100 kg (55, 12) | 16% | 0% | 16% | (7%, 26%) |
| Baseline IGA | | | | |
| Moderate (296, 93) | 27% | 14% | 13% | (5%, 22%) |
| Severe (281, 100) | 15% | 5% | 10% | (4%, 16%) |
| Prior use of immunosuppressants[2] | | | | |
| Yes (264, 84) | 17% | 6% | 11% | (5%, 18%) |
| No (311, 109) | 24% | 12% | 12% | (5%, 20%) |
| Overall | 21% | 9% | 11% | (6%, 17%) |

Source: Statisfical Reviewer's analysis
[1] FAS defined as all randomized subjects who were dosed: Subjects who received rescue medication considered nonresponders; subjects with missing data at Week 16 imputed as nonresponders.
[2] Two subjects in the tralokinumab arm had unknown prior use of immunosuppressants.
Abbreviations: CI, confidence interval; ECZTRA, ECZema TRAlokinumab; FAS, full analysis set; IGA, Investigator's Global Assessment; Q2W, every 2 weeks

**Table 81. EASI-75 Response at Week 16 by Age, Sex, Race, Weight, Baseline IGA Score, and Prior Use of Immunosuppressants—ECZTRA-2 (FAS; Primary Analysis; Primary Estimand[1])**

| Subgroup (n[Tral], n[P]) | Tralokinumab Q2W (N=591) | Placebo (N=201) | Difference | 95% CI |
|---|---|---|---|---|
| Age (years) | | | | |
| 18-64 (548, 186) | 32% | 10% | 23% | (17%, 28%) |
| ≥65 (29, 7) | 38% | 14% | 24% | (-8%, 55%) |
| Sex | | | | |
| Male (347, 108) | 30% | 11% | 19% | (12%, 27%) |
| Female (230, 85) | 36% | 8% | 28% | (19%, 36%) |
| Race | | | | |
| White (370, 123) | 35% | 11% | 25% | (17%, 32%) |
| Non-white (207, 70) | 28% | 9% | 19% | (11%, 28%) |
| Weight | | | | |
| <70 kg (228, 75) | 36% | 8% | 28% | (19%, 37%) |
| 70-100 kg (294, 106) | 31% | 10% | 21% | (13%, 28%) |
| >100 kg (55, 12) | 27% | 17% | 11% | (-13%, 35%) |
| Baseline IGA | | | | |
| Moderate (296, 93) | 28% | 6% | 23% | (14%, 32%) |
| Severe (281, 100) | 37% | 14% | 22% | (15%, 29%) |
| Prior use of immunosuppressants[2] | | | | |
| Yes (264, 84) | 29% | 5% | 24% | (17%, 31%) |
| No (311, 109) | 35% | 14% | 21% | (13%, 30%) |
| Overall | 33% | 10% | 23% | (17%, 28%) |

Source: Statistical Reviewer's analysis; Sites 423 and 435 were removed.
[1] FAS defined as all randomized subjects who were dosed: Subjects who received rescue medication considered nonresponders; subjects with missing data at Week 16 imputed as nonresponders.
[2] Two subjects in the tralokinumab arm had unknown prior use of immunosuppressants.
Abbreviations: CI, confidence interval; EASI-75, at least 75% reduction in Eczema Area and Severity Index score; ECZTRA, ECZema TRAlokinumab; FAS, full analysis set; IGA, Investigator's Global Assessment; Q2W, every 2 weeks

**Table 82. IGA 0/1 Response at Week 16 by Age, Sex, Race, Weight, and Baseline IGA Score—ECZTRA-3 (FAS; Primary Analysis; Primary Estimand[1])**

| Subgroup (n[Tral], n[P]) | Tralokinumab Q2W+TCS (N=243) | Placebo+ TCS (N=123) | Difference | 95% CI |
|---|---|---|---|---|
| Age (years) | | | | |
| 18-64 (231, 115) | 38% | 27% | 11% | (1%, 21%) |
| ≥65 (12, 8) | 33% | 25% | 8% | (32%, 49%) |
| Sex | | | | |
| Male (120, 83) | 34% | 23% | 11% | (-1%, 24%) |
| Female (123, 40) | 41% | 35% | 7% | (-11%, 24%) |
| Race | | | | |
| White (194, 81) | 38% | 32% | 6% | (-6%, 18%) |
| Non-white (49, 42) | 37% | 17% | 20% | (9%, 38%) |
| Weight | | | | |
| <70 kg (91, 38) | 43% | 35% | 6% | (-12%, 24%) |
| 70-100 kg (118, 72) | 34% | 24% | 10% | (-2%, 23%) |
| >100 kg (34, 13) | 38% | 15% | 23% | (-2%, 48%) |
| Baseline IGA | | | | |
| Moderate (127, 64) | 45% | 39% | 6% | (-9%, 21%) |
| Severe (116, 59) | 30% | 14% | 17% | (4%, 29%) |
| Overall | 38% | 27% | 11% | (1%, 21%) |

Source: Statistical Reviewer's analysis; Site 818 was removed.
[1] FAS defined as all randomized subjects who were dosed. Subjects who received rescue medication considered nonresponders; subjects with missing data at Week 16 imputed as nonresponders.
Abbreviations: CI, confidence interval; ECZTRA, ECZema TRAlokinumab; FAS, full analysis set; IGA, Investigator's Global Assessment; Q2W, every 2 weeks; TCS, topical corticosteroids

**Table 83. EASI-75 Response at Week 16 by Age, Sex, Race, and Baseline IGA Score—ECZTRA-3 (FAS; Primary Analysis; Primary Estimand[1])**

| Subgroup (n[Tral], n[P]) | Tralokinumab Q2W+TCS (N=243) | Placebo+ TCS (N=123) | Difference | 95% CI |
|---|---|---|---|---|
| Age (years) | | | | |
| 18-64 (231, 115) | 56% | 36% | 20% | (9%, 31%) |
| ≥65 (12, 8) | 50% | 37% | 12% | (-31%, 56%) |
| Sex | | | | |
| Male (120, 83) | 51% | 30% | 21% | (7%, 34%) |
| Female (123, 40) | 61% | 50% | 11% | (-7%, 29%) |
| Race | | | | |
| White (194, 81) | 55% | 41% | 14% | (2%, 27%) |
| Non-white (49, 42) | 59% | 29% | 31% | (11%, 50%) |
| Weight | | | | |
| <70 kg (91, 38) | 59% | 45% | 15% | (-4%, 33%) |
| 70-100 kg (118, 72) | 53% | 33% | 20% | (6%, 34%) |
| >100 kg (34, 13) | 56% | 31% | 25% | (-5%, 55%) |
| Baseline IGA | | | | |
| Moderate (127, 64) | 57% | 45% | 12% | (-3%, 27%) |
| Severe (116, 59) | 54% | 27% | 27% | (13%, 42%) |
| Overall | 56% | 37% | 19% | (9%, 30%) |

Source: Statistical Reviewer's analysis; Site 818 was removed.
[1] FAS defined as all randomized subjects who were dosed. Subjects who received rescue medication considered nonresponders; subjects with missing data at Week 16 imputed as nonresponders.
Abbreviations: CI, confidence interval; EASI-75, at least 75% reduction in Eczema Area and Severity Index score; ECZTRA, ECZema TRAlokinumab; FAS, full analysis set; IGA, Investigator's Global Assessment; Q2W, every 2 weeks; TCS, topical corticosteroids

**Table 84. IGA 0/1 and EASI-75 Response Rates at Week 16 by Country—ECZTRA-1 (FAS; Primary Analysis; Primary Estimand[1])**

| | IGA 0/1 | | EASI-75 | |
|---|---|---|---|---|
| Country (N[Tral], N[P]) | Tralokinumab Q2W N=601 | Placebo N=197 | Tralokinumab Q2W N=601 | Placebo N=197 |
| Germany (199, 72) | 16% | 6% | 20% | 7% |
| United States (149, 48) | 24% | 17% | 40% | 27% |
| Japan (96, 31) | 2% | 0% | 16% | 10% |
| France (84, 23) | 21% | 4% | 29% | 4% |
| Spain (73, 23) | 11% | 4% | 16% | 13% |
| Overall | 16% | 7% | 25% | 13% |

Source: Statistical Reviewer's analysis.
[1] FAS defined as all randomized subjects who were dosed. Subjects who received rescue medication considered nonresponders; subjects with missing data at Week 16 imputed as nonresponders.
Abbreviations: CI, confidence interval; EASI-75, at least 75% reduction in Eczema Area and Severity Index score; ECZTRA, ECZema TRAlokinumab; FAS, full analysis set; IGA, Investigator's Global Assessment; Q2W, every 2 weeks

**Table 85. IGA 0/1 and EASI-75 Response Rates at Week 16 by Country—ECZTRA-2 (FAS; Primary Analysis; Primary Estimand[1])**

| | IGA 0/1 | | EASI-75 | |
|---|---|---|---|---|
| Country (N[Tral], N[P]) | Tralokinumab Q2W N=577 | Placebo N=193 | Tralokinumab Q2W N=577 | Placebo N=193 |
| Canada (146, 44) | 26% | 5% | 40% | 9% |
| United States (110, 39) | 22% | 18% | 38% | 15% |
| Australia (90, 31) | 6% | 6% | 20% | 10% |
| Poland (67, 27) | 30% | 11% | 34% | 11% |
| Korea (58, 20) | 21% | 5% | 29% | 5% |
| Great Britain (53, 15) | 8% | 7% | 21% | 7% |
| Italy (31, 10) | 52% | 10% | 48% | 0% |
| Russia (14, 5) | 21% | 20% | 14% | 20% |
| Denmark (8, 2) | 13% | 0% | 13% | 0% |
| **Overall** | 21% | 9% | 35% | 10% |

Source: Statistical Reviewer's analysis.
[1] FAS defined as all randomized subjects who were dosed. Subjects who received rescue medication considered nonresponders; subjects with missing data at Week 16 imputed as nonresponders.
Abbreviations: CI, confidence interval; EASI-75, at least 75% reduction in Eczema Area and Severity Index score; ECZTRA, ECZema TRAlokinumab; FAS, full analysis set; IGA, Investigator's Global Assessment; Q2W, every 2 weeks

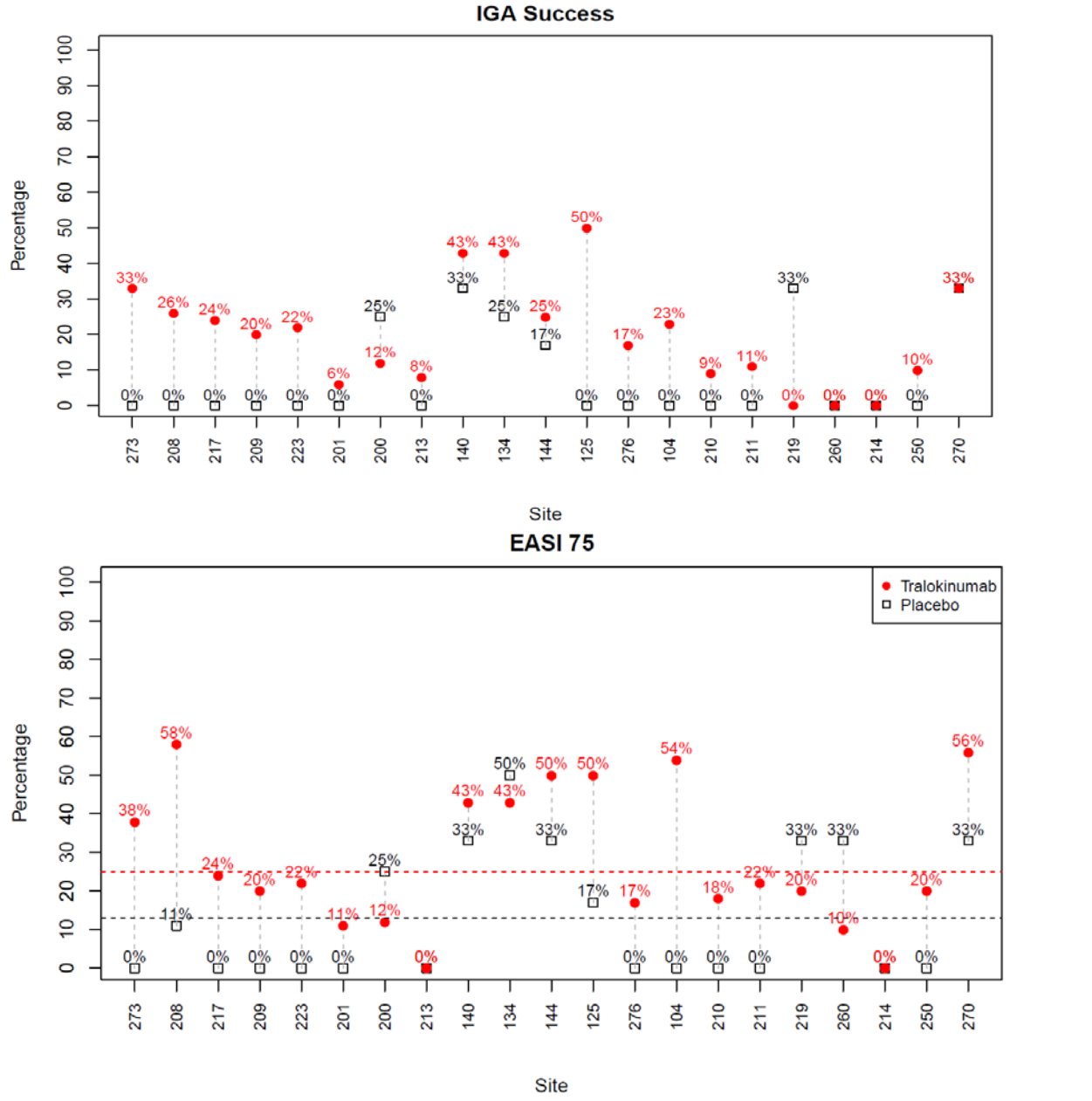
**Table 86. IGA 0/1 and EASI-75 Response Rates at Week 16 by Country—ECZTRA-3 (FAS; Primary Analysis; Primary Estimand[1])**

| | IGA 0/1 | | EASI-75 | |
|---|---|---|---|---|
| Country (N[Tral], N[P]) | Tralokinumab Q2W N=601 | Placebo N=197 | Tralokinumab Q2W N=601 | Placebo N=197 |
| United States (62, 25) | 37% | 12% | 56% | 24% |
| Poland (48, 19) | 40% | 53% | 54% | 47% |
| Canada (34, 26) | 38% | 42% | 62% | 54% |
| Germany (42, 15) | 29% | 13% | 60% | 33% |
| Great Britain (21, 13) | 24% | 8% | 29 | 15% |
| Spain (12, 15) | 83% | 40% | 92% | 53% |
| Belgium (15, 4) | 53% | 0% | 60% | 25% |
| Netherlands (9, 6) | 22% | 0% | 33% | 0% |
| Overall | 38% | 27% | 56% | 37% |

Source: Statistical Reviewer's analysis.
[1] FAS defined as all randomized subjects who were dosed. Subjects who received rescue medication considered nonresponders; subjects with missing data at Week 16 imputed as nonresponders.
Abbreviations: CI, confidence interval; EASI-75, at least 75% reduction in Eczema Area and Severity Index score; ECZTRA, ECZema TRAlokinumab; FAS, full analysis set; IGA, Investigator's Global Assessment; Q2W, every 2 weeks

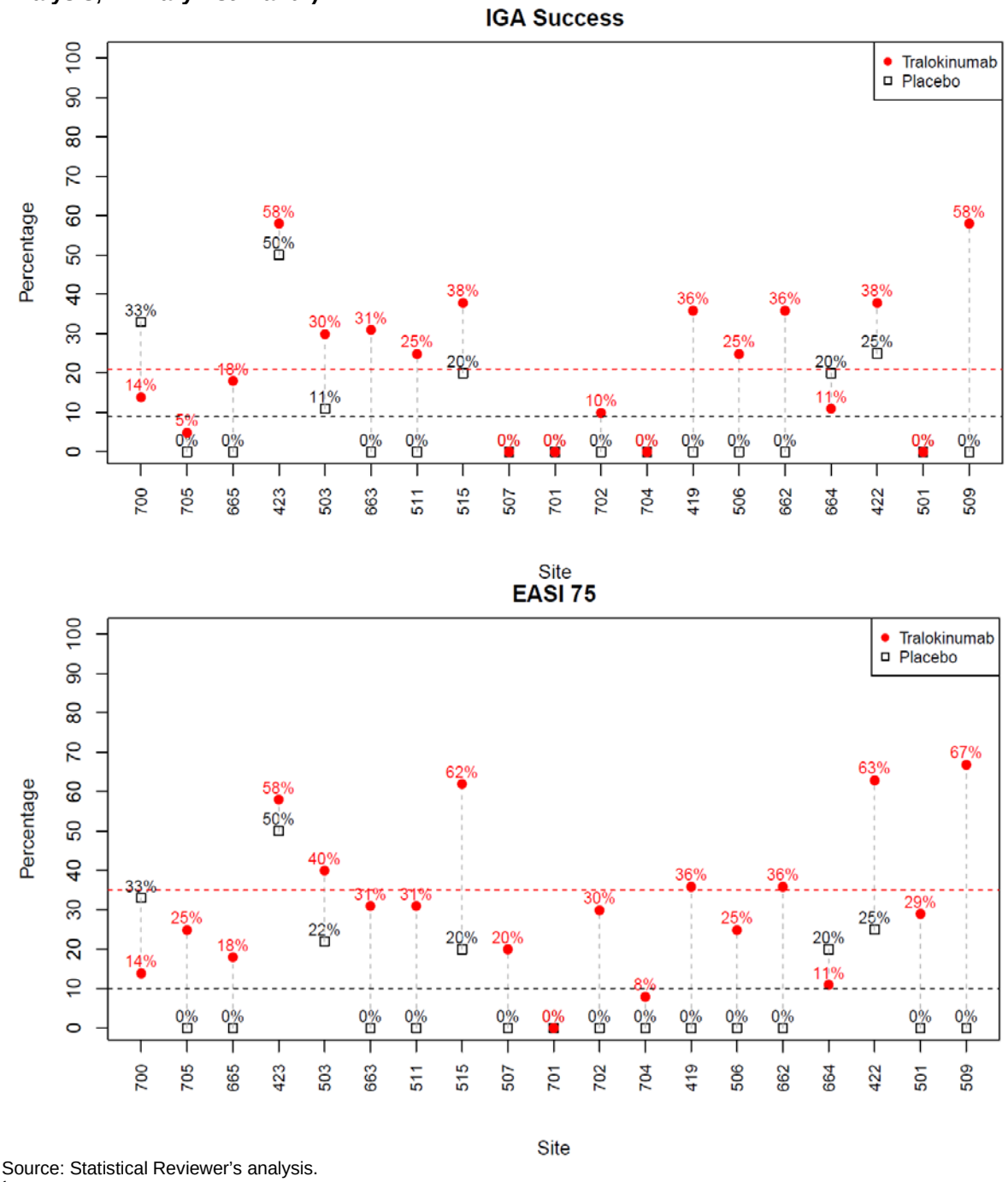
Figure 49, Figure 50, and Figure 51 present the results for the coprimary efficacy endpoints at Week 16 by investigational site. The sites are ordered by total sample size from left to right. Due to the large number of sites, only the results for sites with at least 12 subjects are presented. In all three trials, there was some variability in treatment effect across the sites; however, this may be due to the relatively small sample sizes in several of the sites.

**Figure 49. IGA 0/1 and EASI-75 Response Rates at Week 16 by Site—ECZTRA-1 (FAS; Primary Analysis; Primary Estimand[1])**



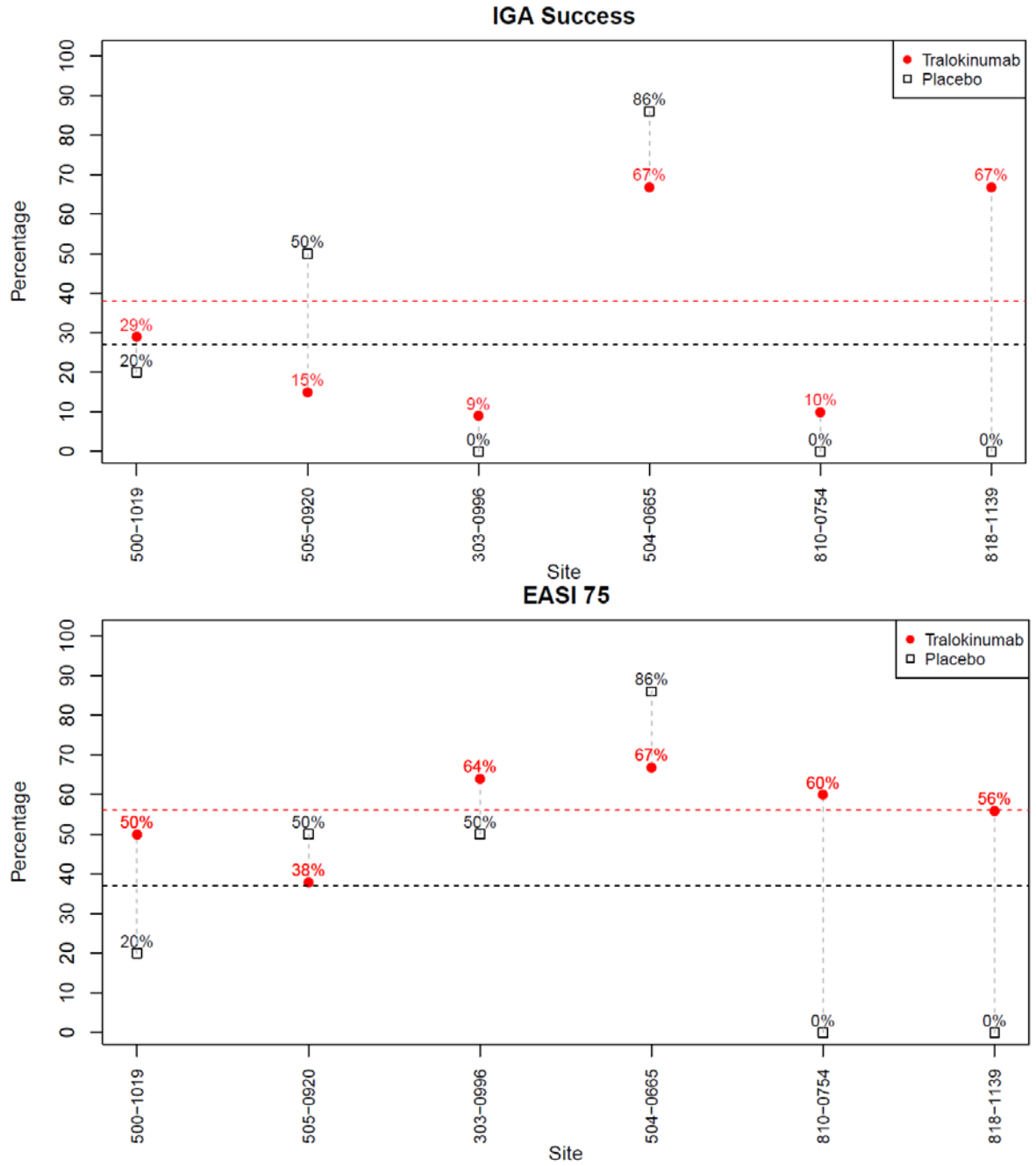

Source: Statistical Reviewer's analysis.
[1] FAS defined as all randomized subjects who were dosed. Subjects who received rescue medication considered nonresponders; subjects with missing data at Week 16 imputed as nonresponders.
Abbreviations: EASI-75, at least 75% reduction in Eczema Area and Severity Index score; ECZTRA, ECZema TRAlokinumab; FAS, full analysis set; IGA, Investigator's Global Assessment; Q2W, every 2 weeks

**Figure 50. IGA 0/1 and EASI-75 Response Rates at Week 16 by Site—ECZTRA-2 (FAS; Primary Analysis; Primary Estimand[1])**




Source: Statistical Reviewer's analysis.
[1] FAS defined as all randomized subjects who were dosed. Subjects who received rescue medication considered nonresponders; subjects with missing data at Week 16 imputed as nonresponders.
Abbreviations: EASI-75, at least 75% reduction in Eczema Area and Severity Index score; ECZTRA, ECZema TRAlokinumab; FAS, full analysis set; IGA, Investigator's Global Assessment; Q2W, every 2 weeks

**Figure 51. IGA 0/1 and EASI-75 Response Rates at Week 16 by Site—ECZTRA-3 (FAS; Primary Analysis; Primary Estimand[1])**




Source: Statistical Reviewer's analysis.
[1] FAS defined as all randomized subjects who were dosed. Subjects who received rescue medication considered nonresponders; subjects with missing data at Week 16 imputed as nonresponders.
Abbreviations: EASI-75, at least 75% reduction in Eczema Area and Severity Index score; ECZTRA, ECZema TRAlokinumab; FAS, full analysis set; IGA, Investigator's Global Assessment; Q2W, every 2 weeks

# 17. Clinical Safety: Additional Information and Assessment

Not applicable.

# 17.1. Death Narratives

The following two deaths were reported during Phase 2 trials in the AD pool:

(1) Phase 2 trial D2213C00001/Subject (b) (6):

A 57-year-old male subject with a medical history of hypertension, cardiac stent placement, and two previous myocardial infarctions received one dose of tralokinumab 45 mg. Two weeks after the first dose, the subject withdrew his consent to participate in the trial and started treatment for AD with cyclosporine and clobetasol propionate cream. Subject was found dead on Day 30 after the first dose of tralokinumab. The attending physician attributed the cause of death to a cardiac event based on patient's history; however, no autopsy was performed. The Investigator considered the event of death as not related to the study drug.

(2) Phase 2 trial ECZTRA-5/Subject (b) (6):

A 50-year-old female subject with multiple comorbidities at screening, including history of hypertension, stroke, schizophrenia, bipolar disorder, gastric bypass surgery, generalized weakness, malnutrition (with 32 pounds weight loss during 7 months prior to screening), thrombocytopenia, emphysema, and chronic obstructive pulmonary disease. Subject was under treatment with over 20 concomitant medications including quetiapine, trifluoperazine, haloperidol, imipramine, and other psychiatric medications. Subject received all doses of tralokinumab and both vaccines at the Week 12 visit per protocol. She lost an additional 13 pounds during Weeks 0 to 12. Laboratory results from Week 12 visit showed hepatic dysfunction with elevated gamma-glutamyl transferase, alanine phosphatase, and LDH.

She was hospitalized 4 days after the Week 12 visit for failure to thrive. No underlying diagnosis or malignancy were identified and she was discharged for rehabilitation to a nursing facility but was readmitted to the hospital after 20 days for progressive weakness, impaired motor function, decreased responsiveness, and speech coherence.

She was readmitted to the hospital with two SAEs of encephalopathy and acute hepatic failure (suspected drug-induced liver injury due to imipramine) with six additional SAEs reported during hospitalization (status epilepticus, respiratory failure, septic shock, pulmonary embolism, pneumonia, and hemorrhagic shock). She died on Day 30 of hospitalization.

According to the autopsy report, the cause of death was septic shock and respiratory failure due to suppurative pneumonia and pulmonary embolism resulting from underlying emphysema with liver disease and malnutrition as contributing factors. Failure to thrive with fatal outcome was assessed as possibly related to tralokinumab. The Investigator did not believe that tralokinumab was the cause of the SAE but could not rule out a causal relationship to weight loss. All eight SAEs were assessed by the Investigator as not related to (tralokinumab or vaccines) due to multiple concomitant medications. The laboratory results suggested a pre-existing liver condition with sudden worsening, but the trend did not correlate with the dates of tralokinumab administration. The Investigator suspected imipramine as possible cause of acute hepatic failure. The hospital physician

suspected concomitant medications imipramine or quetiapine (dose increased prior to onset of the SAEs) likely related to acute hepatic failure and encephalopathy.

The following three deaths were reported in subjects after completion of trials ECZTRA-1 and ECZTRA-2:

(1) ECZTRA-1/Subject (b) (6):

A 51-year-old male subject with a history of hypertension and diabetes mellitus treated with tralokinumab for 42 days experienced pneumonia 444 days after the first dose of open-label tralokinumab and 402 days after the last dose. The subject had withdrawn consent to participate in the trial. He was diagnosed with cutaneous T-cell lymphoma 134 days after the first dose of open-label tralokinumab and was being treated with immunosuppressive therapy with bexarotene and extracorporeal photopheresis when pneumonia was reported.

The Investigator suspected that the subject had most likely suffered from cutaneous T-cell lymphoma for years and had mistakenly been diagnosed with AD.

Subject was hospitalized with pneumonia, cough, dyspnea, and fever, developed acute respiratory distress syndrome and sepsis and was intubated. He developed aseptic cardiomyopathy and received norepinephrine, dobutamine, and plasmapheresis, became comatose, developed shock, and died after 6 days. No autopsy was performed. The cause of death was reported as septic shock. The Investigator considered the event of pneumonia as not related to tralokinumab.

(2) ECZTRA-1/Subject (b) (6)

A 62-year-old male subject with a history of malnutrition and hypercholesterolemia died from myocardial infarction approximately 8 months after the last dose of tralokinumab, following completion of the trial. The subject was reported with an abnormal T wave on an ECG during the trial. No clinical or laboratory tests were reported at the time of the event. The Investigator or Applicant did not suspect tralokinumab as the cause of the event.

(3) ECZTRA-2/Subject (b) (6):

A 24-year-old female subject treated with tralokinumab for 334 days was diagnosed with metastatic squamous cell carcinoma 459 days after the first dose and 108 days after the last dose of tralokinumab.

Approximately 7 months after the first dose of tralokinumab, the subject noted a tongue ulcer, which a specialist evaluated as benign. The subject was withdrawn from the trial 350 days after the first dose of tralokinumab, to be treated with dupilumab. Approximately 3.5 months later she presented at hospital with enlarged lymph nodes and was diagnosed with poorly differentiated metastatic squamous cell carcinoma of the left lateral tongue (nonhuman papillomavirus related) likely from the primary lesion on the tongue. She was hospitalized, underwent surgery, was discharged from the hospital, and underwent chemotherapy and radiotherapy. Her squamous cell carcinoma progressed while receiving chemotherapy and radiotherapy, with metastases found in the liver, bone, and lung. She died 677 days after the first dose of tralokinumab.

The subject had previously received treatment with oral prednisone, methotrexate, cyclosporine, azathioprine, and inhaled corticosteroids for asthma for more than 20 years. She had never smoked and only had only occasional and minimal intake of alcohol. The Investigator evaluated the event as possibly related to tralokinumab (as a contributing factor to her life-long immunosuppression).

***Medical Officer's Assessment***

*The analysis of the likely causes of fatal events appears consistent with the Applicant's conclusion," There is no evidence that treatment with tralokinumab is associated with an increased risk of death compared with placebo." The causes of death in subjects who died during or after the completion of trials in AD does not reveal any serious risks attributable to tralokinumab and are likely a consequence of their comorbid medical conditions or concomitant medications.*

# 17.2. SAE Narratives: Initial Treatment Period—Tralokinumab Group

## ECZTRA-1

**Dermatitis Atopic (4)**

- Subject: (b) (6)
  - Fifty-year-old male hospitalized for severe exacerbation of AD (Day 49). Treatment with tralokinumab was interrupted. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.
- Subject: (b) (6)
  - Thirty-eight-year-old female hospitalized for exacerbation of AD (Day 28). Treatment with tralokinumab was interrupted. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.
- Subject: (b) (6)
  - Forty-six-year-old male hospitalized for severe exacerbation of AD (Day 7). Treatment with tralokinumab was interrupted. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.
- Subject: (b) (6)
  - Thirty-eight-year-old female hospitalized twice for severe exacerbations of AD (Day 15). Treatment with tralokinumab was continued. Outcome was reported as resolving/recovering. Causality per Investigator and per Applicant: not related.

**Accessory Cardiac Pathway (1)**

- Subject: (b) (6)
  - Thirty-eight -year-old male subject, with a reported AE of (orthostatic) syncope during the screening period prior to treatment with tralokinumab, was hospitalized for supraventricular tachycardia (Day 29) and twice underwent catheter ablation. Treatment with tralokinumab was interrupted. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

**Acute Left Ventricular Failure (1)**

- Subject: (b) (6)
  - Fifty-year-old male hospitalized for dyspnea and tachycardia (Day 6). Subject discontinued the trial and lost to follow-up. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

**Alcohol Poisoning (1)**

- Subject: (b) (6)
  - Twenty-nine-year-old male hospitalized for acute alcohol intoxication (Day 97) Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

**Atrial Fibrillation (1)**

- Subject: (b) (6)
  - Thirty-nine-year-old male with baseline ECG showing atrial fibrillation during the screening and baseline visits, referred to cardiology (Day 113), hospitalized for direct current cardioversion followed by radiofrequency catheter ablation. Subject completed the trial. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

**Cellulitis (1)**

- Subject: (b) (6)
  - Fifty-two-year-old male with history of poorly controlled type 2 diabetes, osteomyelitis and toe amputation hospitalized for debridement and IV antibiotics for a left plantar ulcer (Day 44). Lower extremity US (-) for deep vein thrombosis. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

**Eosinophilia (1)**

- Subject: (b) (6)
  - Twenty-one-year-old male with atopic asthma was discontinued from the trial (Day 42) for persistent eosinophilia with AD exacerbation. Eosinophil counts at screening was 800/µL, increased to 1300/µL at randomization, increased to 2900/µL (reported as severe AE) after 2 weeks, and 2600/µL at Week 6. Treatment with tralokinumab was discontinued. Outcome was reported as resolved/recovered. Causality per Investigator possibly related; per Applicant: not related.

**Hyperhidrosis (1)**

- Subject: (b) (6)
  - Sixty-seven-year-old female developed hyperhidrosis and generalized erythema (Day 4) and received treatment with rescue topical diprosone. Treatment with tralokinumab was discontinued (Week 8), and subject was hospitalized (Day 91) for hyperhidrosis. The outcome of the event was reported as recovered (Week 14). Causality per Investigator and per Applicant: probably related.

**Hypertensive Encephalopathy (1)**

- Subject: (b) (6)
  - Fifty-seven-year-old male with history of hypertension hospitalized for hypertensive crisis with encephalopathy. Treatment with tralokinumab was continued. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

**Incarcerated Umbilical Hernia (1)**

- Subject: (b) (6) (same subject reported with an SAE of multiple fractures)
  - Thirty-six-year-old female hospitalized for surgical treatment of an incarcerated umbilical hernia developed after a car accident (Day 76). Treatment with tralokinumab was continued. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

**Injection Site Reaction (1)**

- Subject: (b) (6)
  - Twenty-two-year-old female hospitalized for a severe injection-site erythema, swelling, and warmth at left upper outer thigh (Day 44) and was treated with oral antibiotics for suspected cellulitis, deemed possibly related to tralokinumab. Treatment with tralokinumab was continued. Outcome was reported as resolved/recovered. Rechallenge injection with tralokinumab at a different injection site (left arm) reproduced swelling, tenderness, and warmth (Week 8) of moderate severity that resolved after 24 hr with oral antibiotics and antihistamine. The Investigator did not suspect cellulitis as the SAE. Treatment with tralokinumab was discontinued and subject was withdrawn from trial. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: possibly related.

**Leishmaniasis (1)**

- Subject: (b) (6) (same subject with dermatitis exfoliative generalized)
  - Twenty-nine-year-old male received IV treatment at a clinic for severe cutaneous disseminated leishmaniasis (Day 91).Treatment with tralokinumab was discontinued and subject was withdrawn from trial. Outcome was reported as resolved/recovered. Causality per Investigator: possibly related; causality per Applicant: not related.

**Multiple Fractures (1)**

- Subject: (b) (6) (same subject reported with an SAE of umbilical hernia)
  - Thirty-five-year-old female hospitalized for multiple fractures after a car accident (Day 37). Treatment with tralokinumab was continued. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

**Peripheral Artery Stenosis (1)**

- Subject: (b) (6)
  - Fifty-three-year-old male with history of iliac artery stenosis was hospitalized for iliac artery stent placement (Week 8). Treatment with tralokinumab was continued. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

**Pneumothorax Spontaneous (1)**

- Subject: (b) (6)
  - Fifty-year-old male with history of pneumothorax hospitalized for spontaneous pneumothorax (Day 105) during a flight. Subject was also treated for pneumonia. Treatment with tralokinumab was continued. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

**Stag Horn Calculus (1)**

- Subject: (b) (6)
  - Forty-eight-year-old male with history of nephrolithiasis was hospitalized (Day 95) for renal colic and received treatment with intracorporeal laser lithotripsy. Treatment with tralokinumab was continued. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

**Upper Limb Fracture (1)**

- Subject: (b) (6)
  - Twenty-seven-year-old male hospitalized for left arm fracture related to a sports event (Day 69). Treatment with tralokinumab was continued; however, subject was lost to follow-up and the outcome was reported as unknown. Causality per Investigator and per Applicant: not related.

**Dermatitis Exfoliative Generalized (2)**

- Subject: (b) (6)
  - Forty-one-year-old male with history of diabetes and obesity was hospitalized for suberythroderma (Day 71) and treated with systemic corticosteroids. Treatment with tralokinumab was discontinued and subject withdrew from the trial. Subject had two previous AEs of suberythroderma (first AE with temporal connection to the first tralokinumab injection). Outcome was reported as resolved/recovered. Causality per Investigator: possibly related; causality per Applicant: not related.
- Subject: (b) (6) (same subject with leishmaniasis)
  - Twenty-nine-year-old male hospitalized for erythroderma (Day 136), 37 days after the last dose of tralokinumab (tralokinumab had been discontinued for leishmaniasis). Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

**Asthma (1)**

- Subject: (b) (6)
  - Sixty-nine-year-old male hospitalized for acute asthma exacerbation (Day 60).Treatment with tralokinumab was interrupted. Outcome was reported as resolved/recovered. Causality per Investigator: possibly related; causality per Applicant: not related.

**Bronchitis (1)**

- Subject: (b) (6)
  - Thirty-nine-year-old female with history of asthma hospitalized for dyspnea and bronchitis(no asthma exacerbation reported). Treatment with tralokinumab was interrupted. Outcome was reported as resolved/recovered. Causality per Investigator: probably related; causality per Applicant: not related.

## ECZTRA-2

**Dermatitis Atopic (1)**

- Subject: (b) (6)
  - Thirty-four-year-old male hospitalized for severe exacerbation of AD (Day 14). (Subject was previously hospitalized for AD exacerbation during screening/washout period). Treatment with tralokinumab was continued. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related

**Angiosarcoma (1)**

- Subject: (b) (6)
  - Seventy-four-year-old male with history of right neck squamous cell carcinoma treated with X-ray therapy, hospitalized for surgical excision of post-X-ray therapy angiosarcoma (Day 24). Treatment with tralokinumab was discontinued. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

**Depression Suicidal (1)**

- Subject: (b) (6)
  - Eighteen-year-old male with self-reported history of anxiety and depression (Columbia-Suicide Severity Rating Scale at screening visit documented suicidal behavior prior to screening), presented to the ER for voluntary admission to hospital for severe depression and suicidal ideation, attributed to school and romantic relationship (Day 63). Treatment with tralokinumab was discontinued. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

**Duodenal Ulcer (1)**

- Subject: (b) (6)
  - Fifty-seven-year-old female hospitalized for duodenal ulcer and heartburn (Day 114). Treatment with tralokinumab was continued. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

**Gastroenteritis Viral (1)**

- Subject: (b) (6)
  - Twenty-three-year-old female hospitalized for vomiting and diarrhea (Day 91). Treatment with tralokinumab was continued. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

**Intentional Overdose (1)**

- Subject: (b) (6)
  - Nineteen-year-old male with no psychiatric or drug/alcohol abuse history was hospitalized for intentional drug (Xanax) and alcohol overdose (Week 7). Subject did not have any previous depressive episodes, suicidal ideation, or suicide attempts, and attributed this SAE to social stressors and denied self-injurious behavior. At baseline (prior to treatment initiation), subject's scores on EQ-5D-5L and Hospital and Anxiety Depression Scale indicated presence of depressive and anxiety symptoms. Subject reported onset of a nonserious, moderate AE (preferred term *depression*) on Day 71, and received 3 months of treatment with several medications (antidepressant, anxiolytic, and antipsychotic). Treatment with tralokinumab was continued and subject completed 52 weeks of treatment with tralokinumab. Outcome of AE was reported as not resolved/not recovered. Causality per Investigator and per Applicant: not related.

**Pneumonia (1)**

- Subject: (b) (6)
  - Fifty-year-old male hospitalized for community acquired pneumonia and sepsis (blood cultures positive for *Streptococcus intermedius*) and hypokalemia on (Day 20). Treatment with tralokinumab was discontinued. Outcome was reported as resolved/recovered. Causality per Investigator: possibly related; causality per Applicant: not related.

**Pulmonary Embolism (1)**

- Subject: (b) (6)
  - Thirty-year-old female (with no smoking or family history of venous thromboembolism) was hospitalized for bilateral pulmonary embolism and left pulmonary infarct (Day 35) following a 5 hr flight. Subject requested to be withdrawn from study and treatment with tralokinumab was discontinued. Investigator suspected concomitant ethinylestradiol/desogestrel to be causally related to the event. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

**Squamous Cell Carcinoma of Skin (1)**

- Subject: (b) (6)
  - Fifty-four-year-old male received biopsy and underwent excision of right shin squamous cell carcinoma (Day 71). Lesion was present for 6 months by history. Treatment with tralokinumab was continued. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

**Status Asthmaticus (1)**

- Subject: (b) (6)
  - Eighteen-year-old female with history of asthma and multiple allergies was hospitalized for status asthmaticus (Day 94). Following discharge, she was rehospitalized for status asthmaticus. At Week 14 visit, treatment with tralokinumab was discontinued for lack of efficacy (not for SAE). Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

## ECZTRA-3

**Anaphylactic Reaction (1)**

- Subject: (b) (6)
  - Nineteen-year-old male with history of severe urticaria from cheese was hospitalized for rash and itching after eating a cheeseburger (Day 83). Treatment with tralokinumab was continued. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

**Gastroduodenitis (1)**

- Subject: (b) (6)
  - Forty-six-year-old female with history of Crohn's disease was hospitalized for fever, nausea, and vomiting (presumed as Crohn's exacerbation, diagnosed as Gastroduodenitis on endoscopy) (Day 84). Treatment with tralokinumab was interrupted for one dose, but was resumed at the following visit and subject continued in the study. Outcome was reported as resolving/recovering. Causality per Investigator and per Applicant: not related.

# 17.3. SAE Narratives: Maintenance Treatment Period, Tralokinumab Group

## ECZTRA-1+2 Tralokinumab Q2W

**Diverticulitis (1)—ECZTRA-1 Subject: (b) (6)**

- Forty-one-year-old female hospitalized for abdominal pain (Day 228). Treatment with tralokinumab was continued. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

## ECZTRA-1+2 Tralokinumab Q4W

**Asthma (1)—ECZTRA-1 Subject:** (b) (6)

- Two asthma episodes (same subject with SAE of pneumonia during maintenance and SAE of bronchitis during initial period).
- Thirty-nine-year-old female with history of asthma was hospitalized with severe asthma exacerbation (Day 139). Treatment with tralokinumab (had been temporarily interrupted approximately 4 weeks prior to, and unrelated to this SAE) was continued. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.
- Subject was rehospitalized with moderate asthmatic bronchitis (Week 32). Treatment with tralokinumab (had been temporarily interrupted approximately 2 weeks prior to, and unrelated to this SAE) was continued. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

**Pneumonia (1)—ECZTRA-1 Subject:** (b) (6) **(Same Subject With Asthma)**

- Thirty-nine-year-old female with history of asthma, three prior hospitalizations (one SAE of bronchitis during initial period, one SAE of asthma, and one SAE of asthmatic bronchitis during maintenance period) was hospitalized with moderate pneumonia (Week 36). Treatment with tralokinumab had been temporarily discontinued (unrelated to SAE) was resumed. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

**Intervertebral Disc Protrusion (1)—ECZTRA-1 Subject:** (b) (6)

- Fifty-nine-year-old male hospitalized for SAE of cervical spine disc herniation and pain (Day 224). Treatment with tralokinumab was continued. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

**Pneumothorax Spontaneous (1)—ECZTRA-1 Subject:** (b) (6) **(Same Subject With Same SAE During Initial Period)**

- Fifty-one-year-old male with history of spontaneous pneumothorax was hospitalized for spontaneous pneumothorax of (Day 347). Treatment with tralokinumab was continued. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

**Dizziness (1)—ECZTRA-2 Subject:** (b) (6)

- Eighty-seven-year-old female with history of hypertension, atrial fibrillation on anticoagulant treatment, and dizziness was hospitalized for dizziness that led to a witnessed fall at home (without loss of consciousness) (Day 114). Treatment with tralokinumab was continued. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

**Papillary Thyroid Cancer (1)—ECZTRA-2 Subject:** (b) (6)

- Forty-two-year-old female with history of nodular goiter was hospitalized for thyroidectomy for papillary thyroid cancer (Day 146). Treatment with tralokinumab was discontinued. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

**Schizophrenia (1)—ECZTRA-2 Subject:** (b) (6)

- Twenty-seven-year-old male (with history of prior psychiatric evaluation for strong beliefs related to faith and religion which did not fulfil diagnostic criteria for schizophrenia) was hospitalized for severe schizophrenia (Day 139); subject was discharged (Day 178) and rehospitalized (Day 238). Treatment with tralokinumab was discontinued. Subject was lost to follow-up. Outcome was reported as not resolved/not recovered. Causality per Investigator and per Applicant: not related.

## ECZTRA-3 Tralokinumab Q2W

**Appendicitis (1) Subject:** (b) (6)

- Nineteen-year-old male was hospitalized for acute appendicitis and underwent appendectomy (Day 134). Treatment with tralokinumab was continued. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

**Depression (1) Subject:** (b) (6)

- Sixty-three-year-old male hospitalized for moderate depressive episode with anxiety related to multiple stressors (Day 182). Treatment with tralokinumab was temporarily discontinued. Subject denied suicidal ideation to site staff but expressed suicidal ideation to a psychologist. Subject withdrew from trial visits but planned to enroll in ECZEND trial. Outcome was reported as not resolved/not recovered. Causality per Investigator and per Applicant: not related.

**Gastroenteritis Clostridial (1) Subject:** (b) (6) **(Same Subject With Hypoglycemia)**

- Sixty-four-year-old female with type 2 diabetes, moderate (Day 207). Treatment with tralokinumab was continued. Outcome was reported as resolved/recovered. Causality per Investigator: possibly related, Causality per Applicant: not related.

**Hypoglycemia (1) Subject:** (b) (6) **(Same Subject With Gastroenteritis Clostridial)**

- Sixty-four-year-old female with type 2 diabetes with severe hypoglycemia due to nausea, vomiting, and diarrhea from clostridial gastroenteritis (Day 205). Treatment with tralokinumab was continued. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

**Ligament Rupture (1) Subject:** (b) (6)

- Thirty-seven-year-old female hospitalized for surgical repair of right anterior cruciate ligament after a skiing injury (Day 164). Treatment with tralokinumab was continued. Outcome was reported as resolving/recovering. Causality per Investigator and per Applicant: not related.

**Wrist Fracture (1) Subject:** (b) (6)

- Eighteen-year-old male hospitalized for surgical repair right wrist fracture from a car accident (Day 159). Treatment with tralokinumab was continued. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

### ECZTRA-3 Tralokinumab Q4W

- No SAEs reported.

## 17.4. SAE Narratives: Open-Label Treatment Period, Tralokinumab Q2W+Optional TCS Group

### ECZTRA-1

**Acute Myocardial Infarction (3)**

- Subject: (b) (6)
  - Seventy-five-year-old male with history of type 2 diabetes, hypertension, and hypercholesterolemia was hospitalized for a severe ST segment elevation myocardial infarction (STEMI) and coronary angiography/stent placement (Day 124 of open-label period). Treatment with tralokinumab was discontinued. Subject withdrew from the trial because of sequelae caused by the STEMI. Outcome for STEMI was reported as resolved/recovered with sequelae. Outcome for heart failure from STEMI was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.
- Subject: (b) (6) (subject also with SAE of aortic valve stenosis)
  - Sixty-five-year-old female with history of bicuspid aortic valve and moderate left ventricular hypertrophy, hospitalized for non-STEMI myocardial infarction (Day 53 of open-label period) and atrioventricular replacement for symptomatic severe aortic stenosis. Treatment with tralokinumab was continued. Outcome for nonSTEMI was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

- Subject: (b) (6)
  - Forty-one-year-old male with history of hypertension (and no additional cardiac risk factors) was hospitalized (Day 96 of open-label period) for acute myocardial infarction (transmural) and angioplasty. Treatment with tralokinumab was discontinued. Subject withdrew from the trial for personal reasons. Outcome for SAE was reported as resolved/recovered with sequelae. Causality per Investigator and per Applicant: not related.

**Dermatitis Atopic (4)**

- Subject: (b) (6)
  - Forty-four-year-old male was hospitalized for exacerbation of AD (Day 99 of open-label period). Treatment with tralokinumab was continued. Outcome for SAE was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.
- Subject: (b) (6) (subject also with SAE of hypereosinophilia)
  - Nineteen-year-old male with SAEs of dermatitis atopic and hypereosinophilia. Subject hospitalized (Week 10 of open-label period). Tralokinumab had been discontinued (last dose at Week 6 of open-label period due to the SAE of hypereosinophilia). Outcome for SAE of dermatitis atopic was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.
- Subject (b) (6)
  - Sixty-four-year-old male with 'dermatitis exfoliative generalized' on Day 15 and was hospitalized on Day 20 (the day he received the latest dose) with generalized erythroderma covering a body surface area >90% and was treated with TCS; recovered after three days. Subject was also hospitalized due to 'dermatitis atopic' during screening and safety follow-up (on Day 181). Subject was hospitalized for SAE of atopic dermatitis (Day 62) after one dose of tralokinumab in open-label period. Tralokinumab was discontinued for lack of efficacy. Rescue therapy started prior to SAE. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.
- Subject: (b) (6)
  - Sixty-four-year-old female hospitalized for SAE of AD (Day 56) of maintenance therapy, and subject was transferred to open-label treatment with tralokinumab+optional TCS. Treatment with tralokinumab was continued. Outcome was reported as resolved/recovered. Causality per Investigator: possibly related; causality per Applicant: not related.

**Cellulitis (2)**

- Subject: (b) (6) (subject also with SAE of venous thrombosis)
  - Fifty-two-year-old male with history of was hospitalized for cellulitis of right prepectoral, left ankle and knee (Day 48 open-label period). Treatment with tralokinumab was interrupted. Outcome was reported as resolved/recovered. Causality per Investigator: possibly related; causality per Applicant: not related.
- Subject: (b) (6)
  - Forty-five-year-old male was hospitalized for severe left leg cellulitis (Day 82 of open-label period). Treatment with tralokinumab was discontinued. Outcome was reported as resolved/recovered. Causality per Investigator: probably related; causality per Applicant: not related.

**Invasive Breast Carcinoma (2)**

- Subject: (b) (6)
  - Fifty-year-old female with family history of breast cancer (mother) with invasive left breast carcinoma (Day 42 of open-label period). Treatment with tralokinumab was discontinued. Outcome was reported as resolved/recovered. Causality per Investigator: possibly related; causality per Applicant: not related.
- Subject: (b) (6)
  - Forty-three-year-old female underwent core needle biopsy and diagnosed with invasive left breast carcinoma (ductal carcinoma in situ) (Day 103 of open-label period). Treatment with tralokinumab was discontinued. Outcome was reported as resolving/recovering. Causality per Investigator: possibly related; causality per Applicant: not related.

**Syncope (1)**

- Subject: (b) (6) (subject also with SAE of dehydration)
  - Sixty-seven-year-old male with history of diabetes, hypertension, anemia, and alcohol abuse was hospitalized for syncope (Days 184, 127 of open-label period) presumed related to orthostatic hypotension. Treatment with tralokinumab was continued. Outcome was reported as resolved/recovered. Causality per Investigator: not related; causality per Applicant: not related.

**Aortic Valve Stenosis (1)**

- Subject: (b) (6) (subject also with SAE of acute myocardial infarction)
  - Sixty-five-year-old female with history of bicuspid aortic valve and moderate left ventricular hypertrophy, hospitalized for nonSTEMI myocardial infarction (Day 53 of open-label period) and atrioventricular replacement for symptomatic severe aortic stenosis. Treatment with tralokinumab was continued. Outcome for atrioventricular stenosis was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

**Ataxia (1)**

- Subject: (b) (6)
  - Fifty-one-year-old female with history of migraine and unsteady gait for 10 years was hospitalized for ataxia (no neurological etiology found, ruled out multiple sclerosis and diagnosed with acute depressive episodes with psychosocial fatigue response and somatoform disorder and significant insomnia) (Day 214 of open-label period). Treatment with tralokinumab was continued. Outcome was reported as resolved/recovered. Causality per Investigator: not related; causality per Applicant: not related.

**Carpal Tunnel Syndrome (1)**

- Subject: (b) (6)
  - Fifty-six-year-old male hospitalized for nonelective surgical treatment of carpal tunnel syndrome, with repeat hospitalization approximately 5 months later for arthrodesis and metal implant removal (Day 12 of open-label period). Treatment with tralokinumab was continued. Outcome was reported as resolved/recovered. Causality per Investigator: not related; causality per Applicant: not related.

**Cystitis (1)**

- Subject: (b) (6)
  - Thirty-seven-year-old female (with history of cystitis attributed to immune suppression during treatment with cyclosporine, resolved after discontinuation of cyclosporin) was hospitalized for treatment of chronic cystitis aggravated, moderate severity (Day 43 of open-label period). Treatment with tralokinumab was discontinued (not due to SAE but related to exacerbation of AD and use of prohibited concomitant medication). Outcome was reported as resolved/recovered. Causality per Investigator: possibly related; causality per Applicant: not related.

**Dehydration (1)**

- Subject: (b) (6) (subject also with SAE of syncope)
  - Sixty-seven-year-old male with history of diabetes and hypertension hospitalized for dehydration, alcohol withdrawal, lactic acidosis, and acute kidney injury (Days 209, 154 of open-label period). Treatment with tralokinumab was continued. Outcome was reported as resolved/recovered. Causality per Investigator: not related; causality per Applicant: not related.

**Dermatomyositis (1)**

- Subject: (b) (6)
  - Fifty-five-year-old male with history of prior upper extremity muscle weakness underwent outpatient evaluation of upper back pain, including magnetic resonance imaging and muscle biopsy (Day 292 of open-label period). Treatment with tralokinumab was discontinued. Outcome was reported as not resolved/not recovered. Causality per Investigator: possibly related; causality per Applicant: not related. Subject was hospitalized following treatment of dermatomyositis for elevated liver enzymes due to itraconazole used to treat dermatomyositis during safety follow-up period. Causality of elevated liver function per Investigator: not related; causality per Applicant: not related.

**Eosinophilia (1)**

- Subject: (b) (6) (subject also with SAE of dermatitis atopic)
  - Nineteen-year-old male with history of allergic asthma and multiple environmental allergies reported with an SAE of persistent hypereosinophilia (Day 43 of open-label period). Eosinophil count further increased to 3100/µL (Day 57 of open-label period) (normal range ≤500/µL). Tralokinumab was discontinued and subject was withdrawn from trial. Subject did not receive treatment for hypereosinophilia, and the eosinophil count decreased to 800/µL. Outcome for SAE of hypereosinophilia was reported as resolved/recovered. Causality per Investigator: possibly related; causality per Applicant: possibly related.

**Furuncle (1)**

- Subject: (b) (6)
  - Sixty-year-old female with history of folliculitis (treated topically 2 months prior to event) was hospitalized for treatment of (+) methicillin-resistant *Staphylococcus aureus* furuncles unresponsive to 2 weeks of oral antibiotics therapy (Day 323 of open-label period). Tralokinumab was discontinued and subject was withdrawn from trial. Outcome was reported as resolved/recovered. Causality per Investigator: probably related; causality per Applicant: not related.

**Gastroenteritis Bacterial (1)**

- Subject: (b) (6)
  - Thirty-two-year-old male was hospitalized for bacterial gastroenteritis (Day 55 of open-label period). Tralokinumab was continued. Outcome was reported as resolved/recovered. Causality per Investigator: not related; causality per Applicant: not related.

**Granuloma (1)**

- Subject: (b) (6)
  - Fifty-year-old male hospitalized for necrotizing granulomatous inflammation in right epididymis and radical orchiectomy (Day 169 of open-label period). Tralokinumab was continued. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

**Hemothorax (1)**

- Subject: (b) (6)
  - Thirty-one-year-old male hospitalized for infected hemothorax following a blunt trauma (Day 218 of open-label period). Tralokinumab was continued. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

**Hepatitis (1)**

- Subject: (b) (6)
  - Thirty-one-year-old male with history of renal insufficiency, hypertension, family history of cholecystitis, and normal baseline liver enzymes was hospitalized for icterus, jaundice, change in color of urine and stool and severe hepatitis. Total bilirubin was 9× ULN, bilirubin conjugated 14× ULN, bilirubin unconjugated 2.8× ULN, aspartate aminotransferase 3.3× ULN, alanine aminotransferase 5.8× ULN, alanine phosphatase 1.7× ULN, gamma-glutamyl transferase 2.3× ULN, and INR 1 (Day 27 of open-label period). Tralokinumab was discontinued. Outcome was reported as resolved/recovered. Causality per Investigator (cosuspect: irbesartan): probably related; causality per Applicant: not related. This case was evaluated by an external consultant and attributed to biliary colic and acute cholecystitis, likely transient bile duct obstruction caused by a gallstone that passed spontaneously.

**Hyperglycemia (1)**

- Subject: (b) (6)
  - Thirty-six-year-old female hospitalized for polyuria, polydipsia, and glucose of 550 mg/dL (Day 212 of open-label period). Tralokinumab was discontinued and subject was withdrawn from study. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

**Hyperkalemia (1)**

- Subject: (b) (6)
  - Fifty-three-year-old male with history of diabetes mellitus type 1, hypertension, and chronic renal insufficiency, was hospitalized for hyperkalemia (creatinine 3.31 mg/dl, potassium 6.3 mmol/l, peaked T-waves on ECG) (Day 85 of open-label period). Lisinopril was stopped. Tralokinumab was discontinued and subject withdrew from study. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

**Lens Dislocation (1)**

- Subject: (b) (6)
  - Fifty-five-year-old male hospitalized for lens dislocation of the left eye due to blunt trauma and surgical implantation of a lens (Day 123 of open-label period). Tralokinumab was continued. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

**Liver Disorder (1)**

- Subject: (b) (6)
  - Forty-six-year-old male with history of hepatic function disorder and alcohol use was hospitalized for liver disorder, malaise, and anorexia (Day 282 of open-label period). Tralokinumab was (initially withheld for one week, but after improved liver function noted) continued. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

**Ovarian Cyst Ruptured (1)**

- Subject: (b) (6)
  - Nineteen-year-old female hospitalized for suspected ruptured ovarian cyst and abdominal pain (rule out appendicitis) (Day 141 of open-label period). Tralokinumab was continued. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

**Rotator Cuff Syndrome (1)**

- Subject: (b) (6)
  - Forty-nine-year-old female with history of left shoulder pain was hospitalized for surgical left shoulder joint replacement and repair of rotator cuff. Tralokinumab was continued. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

**Ulcerative Keratitis (1)**

- Subject: (b) (6)
  - Fifty-two-year-old female with history of allergic conjunctivitis, recurrent facial herpes simplex virus, no history of keratitis (not using contact lens) was hospitalized for corneal ulcer/ corneal infiltrate of left eye (*S. aureus* (+) culture). Tralokinumab was discontinued. Outcome was reported as resolved/recovered. Causality per Investigator: possibly related; causality per Applicant: not related. Rationale for the Investigator's related causality is that the patient had three nonserious AEs of conjunctivitis and two AEs of eye pain following prior tralokinumab injections.

**Venous Thrombosis (1)**

- Subject: (b) (6) (subject also with SAE: cellulitis)
  - Fifty-two-year-old male hospitalized for cellulitis of right prepectoral, left ankle, and knee (Day 48 open-label period). Venous thrombosis of left subclavian, brachiocephalic, internal jugular, and superior vena cava diagnosed during evaluation of cellulitis. Treatment with tralokinumab was discontinued. Outcome was reported as resolved/recovered. Causality per Investigator: possibly related; causality per Applicant: not related.

## ECZTRA-2

**Dermatitis Atopic (1)**

- Subject: (b) (6)
  - Fifty-four-year-old male hospitalized for AD exacerbation and oral steroid therapy (Day 71 of open-label period). Tralokinumab was discontinued. And subject was withdrawn from trial. Outcome was reported as resolved/recovered. Causality per Investigator: possibly related; causality per Applicant: not related.

**Syncope (1)**

- Subject: (b) (6) (subject also with SAE of neurological symptom)
  - Seventy-eight-year-old male hospitalized for vasovagal syncope (Day 13 of open-label period). Tralokinumab was continued. Outcome was reported as resolved/recovered. Causality per Investigator not related; causality per Applicant: not related.

**Anaphylactic Reaction (2)**

- Subject: (b) (6)
  - Thirty-nine-year-old female with history of two anaphylactic reactions (unknown cause) hospitalized(treated with intramuscular adrenaline and antihistamine by mouth) for sudden onset of throat pain, lip swelling, abdominal pain, nausea, hives and whole-body itching after eating pizza with salmon (Day 23 of open-label period). Tralokinumab was continued. Outcome was reported as resolved/recovered. Causality per Investigator; causality per Applicant: not related.
- Subject: (b) (6)
  - Fifty-five-year-old male with history of asthma hospitalized (treated with adrenaline IV and oral steroid) for bee sting leading to sudden onset of generalized itching, oral numbness, swelling of soft palate/nasal passages, and change of voice (Day 58 of open-label period). Tralokinumab was continued. Outcome was reported as resolved/ recovered. Causality per Investigator and per Applicant: not related.

**Asthma (1)**

- Subject: (b) (6) (subject also with SAE of pneumonia)
  - Thirty-three-year-old male with history of pneumonia and pulmonary aspergillosis was hospitalized for severe asthma exacerbation (Day 47 of open-label period). Tralokinumab was continued. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

**Benign Ethnic Neutropenia (1)**

- Subject: (b) (6)
  - Thirty-four-year-old male developed asymptomatic neutropenia (1200/µL); no therapy was given (Day 72 of open-label period). Tralokinumab was continued. Outcome was reported as not resolved/not recovered. Causality per Investigator: possibly related; causality per Applicant: not related.

**Device Dislocation (1)**

- Subject: (b) (6)
  - Thirty-year-old male with history of cataract surgery and retinal detachment was hospitalized for surgical treatment of intraocular lens luxation (Day 125 of open-label period). Tralokinumab was continued. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

**Facial Bones Fracture (1)**

- Subject: (b) (6)
  - Fifty-one-year-old female hospitalized for surgical treatment of facial bone fracture related to an accidental fall (Day 98 of open-label period). Tralokinumab was continued. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

**Head Injury (1)**

- Subject: (b) (6)
  - Twenty-year-old male hospitalized for multiple traumatic injuries related to car accident (Week 22 of open-label period). Tralokinumab was discontinued. Outcome was reported as resolved/recovered with residual symptoms. Causality per Investigator and per Applicant: not related.

**Keratitis Viral (1)**

- Subject: (b) (6)
  - Fifty-nine-year-old male with ongoing AE of conjunctivitis (since Day 33 of open-label period) was hospitalized for severe keratitis (suspected viral, (+) methicillin-susceptible *S. aureus* culture; Day 71 of open-label period). Tralokinumab was continued. Outcome was reported as resolved/recovered. Causality per Investigator probably related; causality per Applicant: not related.

**Neurological Symptom (1)**

- Subject: (b) (6) (subject also with SAE of syncope)
  - Seventy-eight-year-old male underwent neurological evaluation for fatigue, lack of concentration, confusion, shuffling gait, and left-sided weakness (Day 52 of open-label period). Tralokinumab was continued. Outcome was reported as not resolved/not recovered. Subject withdrew from trial (not due to SAE). Causality per Investigator and per Applicant: not related.

**Ovarian Cystectomy (1)**

- Subject: (b) (6)
  - Twenty-nine-year-old female with history of ovarian cysts hospitalized for laparotomy and excision of ovarian cysts (Week 22 of open-label period). Tralokinumab was continued. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

**Photosensitivity Reaction (1)**

- Subject: (b) (6)
  - Sixty-seven-year-old female with history of photo drug eruption (clinically diagnosed with inconclusive biopsy) was hospitalized for exacerbation of photo drug eruption (suspected drugs: fluoxetine, Stilnox, and atorvastatin) and treated with prednisone taper (Day 99 of open-label period). Tralokinumab was discontinued and subject was withdrawn from trial. Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

**Pneumonia (1)**

- Subject: (b) (6) (subject also with SAE of asthma)
  - Thirty-three-year-old male hospitalized for lobar pneumonia (Day 26 of open-label period). Tralokinumab was continued (after withholding one dose). Outcome was reported as resolved/recovered. Causality per Investigator; causality per Applicant: not related.

**Radius Fracture (1)**

- Subject: (b) (6)
  - Sixty-two-year-old female treated for right distal radius fracture related to an accidental fall (Day 224 of open-label period) with plaster cast, and surgical open reduction internal fixation 3 weeks later. Tralokinumab was discontinued (due to completion of trial; not related to SAE). Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

**Retinal Detachment (1)**

- Subject: (b) (6)
  - Twenty-four-year-old male hospitalized for surgical treatment of left retinal detachment (Day 58 of open-label period). Tralokinumab was continued. Outcome was reported as resolving/recovering. Causality per Investigator; causality per Applicant: not related.

**Road Traffic Accident (1)**

- Subject: (b) (6)
  - Fifty-year-old female hospitalized head trauma related to car accident (Day 79 of open-label period). Tralokinumab was continued. Outcome was reported as (stabilized) resolving/recovering. Causality per Investigator; causality per Applicant: not related.

**Staphylococcal Bacteremia (1)**

- Subject: (b) (6)
  - Nineteen-year-old male hospitalized for AD exacerbation, *S. aureus* skin infection, and bacteremia (Day 252 of open-label period). Tralokinumab was not discontinued (last scheduled dose had been administered at Week 50 [prior to SAE]). Outcome was reported as resolved/recovered. Causality per Investigator and per Applicant: not related.

# 17.5. TEAEs by Subgroup-Initial Treatment Period, Monotherapy Trials ECZTRA-1 and ECZTRA-2

The Applicant conducted safety analyses based on demographic subgroups (age category, sex, race, ethnicity) as well as baseline disease severity (IGA of 3 or 4) and geographic region. The results indicated that there were no substantial differences in the risk of AEs in any subgroup.

However, because the trials were not powered for these analyses, the data must be interpreted with caution. TEAEs by demographic subgroups are presented below.

## TEAEs By Sex

The frequency of TEAEs by each category reported in the tralokinumab group was similar between male and female subjects and similar or lower than the corresponding placebo groups (Table 87).

**Table 87. AEs During the Initial Treatment Period, Subgroup Analysis by Sex, Safety Population, ECZTRA-1 and ECZTRA-2**

| | (b) (4) Monotherapy Pool (ECZTRA-1 and ECZTRA-2) | | | |
|---|---|---|---|---|
| | Tralokinumab Q2W N=1194 | | Placebo N=396 | |
| AE | F N=485 | M N=709 | F N=161 | M N=235 |
| Any AE | 337 (69.5) | 487 (68.7) | 120 (74.5) | 163 (69.4) |
| Moderate or severe AE | 189 (39.0) | 242 (34.1) | 89 (55.3) | 104 (44.3) |
| Any SAE | 9 (1.9) | 24 (3.4) | 5 (3.1) | 8 (3.4) |
| SAE with fatal outcome | 0 | 0 | 0 | 0 |
| AE leading to discontinuation of study drug | 14 (2.9) | 15 (2.1) | 3 (1.9) | 8 (3.4) |
| AE leading to dose modification of study drug | 20 (4.1) | 24 (3.4) | 11 (6.8) | 19 (8.1) |
| AE leading to interruption of study drug | 19 (3.9) | 24 (3.4) | 11 (6.8) | 19 (8.1) |
| AE leading to reduction of study drug | 1 (0.2) | 0 | 0 | 0 |
| AE leading to delay of study drug | 0 | 0 | 0 | 0 |

Source: Analysis by the clinical data safety reviewer for BLA 761180.
Abbreviations: (b) (4) tralokinumab; AE, adverse event; ECZTRA, ECZema TRAlokinumab; F, female; M, male; Q2W, every 2 weeks; SAE, serious adverse event

## TEAEs By Age

The frequency of TEAEs by each category reported in the tralokinumab group was generally lower in subjects ≥65 years of age than younger subjects (age groups 18 to 64 years) and similar or lower than the corresponding placebo groups as listed in Table 88.

**Table 88. AEs During the Initial Treatment Period, Subgroup Analysis, by Age, Safety Population, ECZTRA-1 and ECZTRA-2**

| | (b) (4) Monotherapy Pool (ECZTRA-1 and ECZTRA-2) | | | |
|---|---|---|---|---|
| | Tralokinumab Q2W N=1194 | | Placebo N=396 | |
| Event | 18-64 Years N=1135 | ≥65 Years N=59 | 18-64 Years N=375 | ≥65 Years N=21 |
| Any AE | 789 (69.5) | 35 (61.4) | 270 (72.0) | 13 (61.9) |
| Moderate or severe AE | 418 (36.8) | 13 (22.8) | 184 (49.1) | 9 (42.9) |
| Any SAE | 30 (2.6) | 3 (5.3) | 10 (2.7) | 3 (14.3) |
| SAE with fatal outcome | 0 | 0 | 0 | 0 |
| AE leading to discontinuation of study drug | 26 (2.3) | 3 (5.3) | 9 (2.4) | 2 (9.5) |
| AE leading to dose modification of study drug | 43 (3.8) | 1 (1.8) | 26 (6.9) | 4 (19.0) |
| AE leading to interruption of study drug | 42 (3.7) | 1 (1.8) | 26 (6.9) | 4 (19.0) |
| AE leading to reduction of study drug | 1 (0.1) | 0 | 0 | 0 |
| AE leading to delay of study drug | 0 | 0 | 0 | 0 |

Source: Analysis by the clinical data safety reviewer for BLA 761180.
Abbreviations: (b) (4) tralokinumab; AE, adverse event; ECZTRA, ECZema TRAlokinumab; Q2W, every 2 weeks; SAE, serious adverse event

## TEAEs By Race

The frequency of TEAEs by each category reported in the tralokinumab group was generally lower for all races compared to their corresponding placebo groups. African American subjects had lower reported TEAE frequencies compared to other races in both tralokinumab and placebo groups, as listed in Table 89.

**Table 89. AEs During the Initial Treatment Period, Subgroup Analysis by Race, Safety Population, ECZTRA-1 and ECZTRA-2**

| | (b) (4) Monotherapy pool (ECZTRA 1 and ECZTRA2) Tralokinumab Q2W N=1194 | | | | | | | (b) (4) Monotherapy pool (ECZTRA 1 and ECZTRA2) placebo N=396 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | RACE-AMERICAN INDIAN OR ALASKA NATIVE N=3 | RACE-ASIAN N=275 | RACE-BLACK OR AFRICAN AMERICAN N=84 | RACE-NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER N=6 | RACE-OTHER N=27 | RACE-WHITE N=797 | RACE-MISSING N=2 | RACE-AMERICAN INDIAN OR ALASKA NATIVE N=0 | RACE-ASIAN N=91 | RACE-BLACK OR AFRICAN AMERICAN N=34 | RACE-NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER N=1 | RACE-OTHER N=9 | RACE-WHITE N=259 | RACE-MISSING N=3 |
| Event | | | | | | | | | | | | | | |
| Any AE | 3 (100.0) | 185 (67.3) | 36 (42.9) | 5 (83.3) | 20 (74.1) | 573 (71.9) | 2 (100.0) | 0 | 66 (72.5) | 19 (55.9) | 0 | 8 (88.9) | 187 (72.2) | 3 (100.0) |
| Moderate or severe AEs | 2 (66.7) | 77 (28.0) | 14 (16.7) | 2 (33.3) | 8 (29.6) | 326 (40.9) | 2 (100.0) | 0 | 39 (42.9) | 9 (26.5) | 0 | 7 (77.8) | 138 (53.3) | 0 |
| Any SAE | 0 | 5 (1.8) | 2 (2.4) | 0 | 2 (7.4) | 24 (3.0) | 0 | 0 | 0 | 3 (8.8) | 0 | 0 | 10 (3.9) | 0 |
| SAE with fatal outcome | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| AE leading to discontinuation of study drug | 0 | 7 (2.5) | 4 (4.8) | 0 | 1 (3.7) | 17 (2.1) | 0 | 0 | 2 (2.2) | 1 (2.9) | 0 | 0 | 8 (3.1) | 0 |
| AE leading to dose modification of study drug | 0 | 9 (3.3) | 1 (1.2) | 1 (16.7) | 1 (3.7) | 31 (3.9) | 1 (50.0) | 0 | 4 (4.4) | 1 (2.9) | 0 | 1 (11.1) | 24 (9.3) | 0 |
| AE leading to interruption of study drug | 0 | 8 (2.9) | 1 (1.2) | 1 (16.7) | 1 (3.7) | 31 (3.9) | 1 (50.0) | 0 | 4 (4.4) | 1 (2.9) | 0 | 1 (11.1) | 24 (9.3) | 0 |
| AE leading to reduction of study drug | 0 | 1 (0.4) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| AE leading to delay of study drug | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Source: Analysis by the clinical data safety reviewer for BLA 761180.
Abbreviations: (b) (4) tralokinumab; AE, adverse event; ECZTRA, ECZema TRAlokinumab; Q2W, every 2 weeks; SAE, serious adverse event

## TEAEs By Ethnicity

The frequency of TEAEs by each category reported in the tralokinumab group was similar between Hispanic and non-Hispanic groups and similar or less than the corresponding placebo groups (except for a lower frequency of any AE category in the Hispanic placebo group, which was attributed to a lower reported frequency of zero for the preferred term of viral upper respiratory infection) as listed in Table 90.

**Table 90. AEs During the Initial Treatment Period, Subgroup Analysis, by Ethnicity, Safety Population, ECZTRA-1 and ECZTRA-2**

| | (b) (4) Monotherapy Pool (ECZTRA-1 and ECZTRA-2) | | | | | |
|---|---|---|---|---|---|---|
| | Tralokinumab Q2W N=1194 | | | Placebo N=396 | | |
| Event | Hispanic or Latino N=67 | Not Hispanic or Latino N=1125 | Missing N=2 | Hispanic or Latino N=25 | Not Hispanic or Latino N=368 | Missing N=3 |
| Any AE | 48 (71.6) | 774 (68.8) | 2 (100.0) | 15 (60.0) | 265 (72.0) | 3 (100.0) |
| Moderate or severe AE | 22 (32.8) | 407 (36.2) | 2 (100.0) | 11 (44.0) | 182 (49.5) | 0 |
| Any SAE | 1 (1.5) | 32 (2.8) | 0 | 0 | 13 (3.5) | 0 |
| SAE with fatal outcome | 0 | 0 | 0 | 0 | 0 | 0 |
| AE leading to discontinuation of study drug | 2 (3.0) | 27 (2.4) | 0 | 1 (4.0) | 10 (2.7) | 0 |
| AE leading to dose modification of study drug | 2 (3.0) | 41 (3.6) | 1 (50.0) | 2 (8.0) | 28 (7.6) | 0 |
| AE leading to interruption of study drug | 2 (3.0) | 40 (3.6) | 1 (50.0) | 2 (8.0) | 28 (7.6) | 0 |
| AE leading to reduction of study drug | 0 | 1 (0.1) | 0 | 0 | 0 | 0 |
| AE leading to delay of study drug | 0 | 0 | 0 | 0 | 0 | 0 |

Source: Analysis by the clinical data safety reviewer for BLA 761180.
Abbreviations: (b) (4) tralokinumab; AE, adverse event; ECZTRA, ECZema TRAlokinumab; Q2W, every 2 weeks; SAE, serious adverse event

## TEAEs By Baseline IGA Score (3 or 4)

The frequency of TEAEs by category reported was similar or lower in the tralokinumab group compared to the corresponding placebo group with the same baseline IGA. Within the same treatment groups, TEAEs were reported at higher frequencies for subjects with an IGA score of 4, compared to those with an IGA score of 3 at baseline, as listed in Table 91.

**Table 91. AEs During the Initial Treatment Period, Subgroup Analysis by Baseline Disease Severity (IGA Score), Safety Population, ECZTRA-1 and ECZTRA-2**

| | [redacted] Monotherapy Pool (ECZTRA-1 and ECZTRA-2) | | | |
|---|---|---|---|---|
| | Tralokinumab Q2W N=1194 | | Placebo N=396 | |
| Event | IGA 3.0 N=602 | IGA 4.0 N=592 | IGA 3.0 N=194 | IGA 4.0 N=202 |
| Any AE | 390 (64.8) | 434 (73.3) | 125 (64.4) | 158 (78.2) |
| Moderate or severe AE | 191 (31.7) | 240 (40.5) | 81 (41.8) | 112 (55.4) |
| Any SAE | 9 (1.5) | 24 (4.1) | 2 (1.0) | 11 (5.4) |
| SAE with fatal outcome | 0 | 0 | 0 | 0 |
| AE leading to discontinuation of study drug | 10 (1.7) | 19 (3.2) | 2 (1.0) | 9 (4.5) |
| AE leading to dose modification of study drug | 24 (4.0) | 20 (3.4) | 7 (3.6) | 23 (11.4) |
| AE leading to interruption of study drug | 23 (3.8) | 20 (3.4) | 7 (3.6) | 23 (11.4) |
| AE leading to reduction of study drug | 1 (0.2) | 0 | 0 | 0 |
| AE leading to delay of study drug | 0 | 0 | 0 | 0 |

Source: Analysis by the clinical data safety reviewer for BLA 761180.
Abbreviations: [redacted] tralokinumab; AE, adverse event; ECZTRA, ECZema TRAlokinumab; IGA, Investigator's Global Assessment; Q2W, every 2 weeks; SAE, serious adverse event

## TEAEs By Geographic Region

The frequency of TEAEs by each category reported in the tralokinumab group was similar to or lower compared to the corresponding placebo group for all geographic regions, with a trend towards lower frequencies of reported TEAEs for North America compared to other regions (regardless of treatment group), as listed in Table 92.

**Table 92. AEs During the Initial Treatment Period, Subgroup Analysis, by Region, Safety Population, Trials ECZTRA-1 and ECZTRA-2**

| | [redacted] Monotherapy Pool (ECZTRA-1 and ECZTRA-2) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Tralokinumab Q2W N=1194 | | | | | Placebo N=396 | | | | |
| Event | Asia N=59 | Australia N=90 | Europe N=530 | Japan N=96 | North America N=419 | Asia N=19 | Australia N=31 | Europe N=176 | Japan N=31 | North America N=139 |
| Any AE | 25 (42.4) | 71 (78.9) | 417 (78.7) | 79 (82.3) | 232 (55.4) | 11 (57.9) | 28 (90.3) | 134 (76.1) | 27 (87.1) | 83 (59.7) |
| Moderate or severe AE | 9 (15.3) | 32 (35.6) | 248 (46.8) | 38 (39.6) | 104 (24.8) | 5 (26.3) | 15 (48.4) | 97 (55.1) | 16 (51.6) | 60 (43.2) |
| Any SAE | 0 | 2 (2.2) | 20 (3.8) | 3 (3.1) | 8 (1.9) | 0 | 2 (6.5) | 7 (4.0) | 0 | 4 (2.9) |
| SAE with fatal outcome | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| AE leading to discontinuation of study drug | 2 (3.4) | 1 (1.1) | 13 (2.5) | 2 (2.1) | 11 (2.6) | 1 (5.3) | 0 | 8 (4.5) | 1 (3.2) | 1 (0.7) |
| AE leading to dose modification of study drug | 3 (5.1) | 1 (1.1) | 24 (4.5) | 2 (2.1) | 14 (3.3) | 2 (10.5) | 3 (9.7) | 17 (9.7) | 0 | 8 (5.8) |
| AE leading to interruption of study drug | 3 (5.1) | 0 | 24 (4.5) | 2 (2.1) | 14 (3.3) | 2 (10.5) | 3 (9.7) | 17 (9.7) | 0 | 8 (5.8) |
| AE leading to reduction of study drug | 0 | 1 (1.1) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| AE leading to delay of study drug | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Source: Analysis by the clinical data safety reviewer for BLA 761180.
Abbreviations: [redacted] tralokinumab; AE, adverse event; ECZTRA, ECZema TRAlokinumab; IGA, Investigator's Global Assessment; Q2W, every 2 weeks; SAE, serious adverse event

# 18. Mechanism of Action/Drug Resistance: Additional Information and Assessment

Not applicable for this application.

# 19. Other Drug Development Considerations: Additional Information and Assessment

None.

# 20. Data Integrity-Related Consults (Office of Scientific Investigations, Other Inspections)

The Office of Scientific Investigations (OSI) conducted clinical trial site inspections to ensure the quality and reliability of the data from the ECZTRA-1, -2, and -3 trials, which were submitted in support of BLA 761180.

The following four clinical trial sites were selected by the OSI for inspections using a risk-based approach, including number of enrolled subjects, site efficacy, protocol deviations, and prior inspectional history.

- Site 273 (Jean-Philippe Lacour in Nice, France) for ECZTRA-1: Inspection of this site could not be completed due to coronavirus disease-2019–related restrictions on international travel.
- Site 125 (Dr. Nguyen) for ECZTRA-1.

Records reviewed during the inspection included, but not limited to, informed consent, financial disclosures, screening logs, AE reporting, primary endpoint data, concomitant medications, institutional review board (IRB) approvals, correspondence, training records, and protocol deviations.

The FDA field investigator reviewed the records of all 16 randomized subjects for verification of the primary efficacy endpoint data. There was only one discrepancy noted (the Applicant attributed the discrepancy to a data entry error).

- Site 810 (Dr. Alexis) for ECZTRA-3.

Records reviewed during the inspection included, but were not limited to, informed consent, eligibility, protocol adherence, AE reporting, delegation of authority, financial disclosure, IRB approvals, training logs, notes to file, and investigational product accountability/handling.

The primary efficacy endpoint data were verified for all 13 randomized subjects; no discrepancies were noted. There were no SAEs reported at this site, and there was no evidence of under-reporting of AEs.

- Site 423 (Dr. Parish) for ECZTRA-2.

At this site, 25 subjects were screened, and 20 subjects were enrolled and randomized. This site was terminated for noncompliance by the Applicant during the trial, at which time 14 subjects had completed the Week 16 assessments. Of note, OSI had not been informed that this site had been terminated at the time of the site selection meeting and issuance of the assignment memo.

Records reviewed during the inspection included, but not limited to, FDA Form 1572 documentation, training, delegation of authority, informed consent, subject eligibility, efficacy endpoint data, AEs, monitoring reports, IRB approvals and correspondence, record retention policy, and investigational product accountability (receipt, storage, administration, and disposition records).

The primary efficacy endpoint data (EASI and IGA) for all 14 subjects who completed the Week 16 assessments before the site was terminated by the Applicant were verified; no discrepancies were noted. However, review of the source data for these endpoints showed that the clinical investigator used a scribe (his study coordinator, who would never sign) to record EASI scores, and this (and other documentation) frequently lacked clinical investigator signatures, initials, and/or dates, or this information was added up to 2 weeks after the assessment was performed. The inspection also noted multiple out of window visits.

A potential blinding issue was also noted. There were no SAEs reported at the site. Also, there was no evidence of underreporting of AEs. However, site monitoring reports documented that several AE entries were missing dates and signatures.

The OSI team inspected the three domestic sites and recommended the following:

- Based on the results of the Drs. Alexis and Nguyen inspections, the studies LP0162-1325 (ECZTRA-1) and LP0162-1339 (ECZTRA-3) appear to have been conducted adequately, and the data generated by these sites appears acceptable in support of the respective indication.
- Dr. Parish's Site 423 had been terminated by the Applicant during the trial for noncompliance. The OSI team recommended the following:

"Due to concerns related to study conduct, potential unblinding, and data integrity and reliability noted during the inspection of Dr. Parish's site (in particular with regard to the Week 16 EASI scores), we recommend a sensitivity analysis be conducted with regard to the data from this site."

Statistical analyses excluding this site did not affect the statistical conclusions regarding efficacy of the product.

# 21. Labeling Summary of Considerations and Key Additional Information

Since the recommendation of this review is for a complete response, labeling negotiations were not completed. However, labeling interactions with the Applicant are largely complete and can be finalized during a successful later cycle for this application.

# 22. Postmarketing Requirements and Commitments

As a complete response is recommended for this application, these postmarketing requirements (PMRs) are proposed to be included once the current deficiencies in the application are satisfactorily addressed, and an approval for the application for licensure can be recommended:

1. For the pregnancy exposure registry, the PMR description should include the following:

A prospective, registry-based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to tralokinumab during pregnancy to an unexposed control population. (b) (4)

This review agrees with the Applicant's proposed plan for a retrospective cohort study using electronic medical record data, and recommends the following PMR description:

An additional pregnancy study that uses a different design from the Pregnancy Registry (for example a retrospective cohort study using claims or electronic medical record data with outcome validation or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to tralokinumab during pregnancy compared to an unexposed control population.

# 23. Financial Disclosure

**Table 93. Covered Clinical Studies: [LP0162-1325 (ECZTRA-1)]**

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from Applicant) |
| Total number of investigators identified: 126 | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1 | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0<br>Significant payments of other sorts: 1<br>Proprietary interest in the product tested held by investigator: 0<br>Significant equity interest held by investigator: 0<br>Sponsor of covered study: LEO Pharma | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes ☒ | No ☐ (Request details from Applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes ☒ | No ☐ (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3): 1 | | |
| Is an attachment provided with the reason: | Yes ☒ | No ☐ (Request explanation from Applicant) |

**Table 94. Covered Clinical Studies: [LP0162-1326 (ECZTRA-2)]**

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from Applicant) |
| Total number of investigators identified: 114 | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1 | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0<br>Significant payments of other sorts: 1<br>Proprietary interest in the product tested held by investigator: 0<br>Significant equity interest held by investigator: 0<br>Sponsor of covered study: LEO Pharma | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes ☒ | No ☐ (Request details from Applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes ☒ | No ☐ (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3): 1 | | |
| Is an attachment provided with the reason: | Yes ☒ | No ☐ (Request explanation from Applicant) |

**Table 95. Covered Clinical Studies: [LP0162-1339 (ECZTRA-3)]**

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from Applicant) |
| Total number of investigators identified: 69 | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0 | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0<br>Significant payments of other sorts: 0<br>Proprietary interest in the product tested held by investigator: 0<br>Significant equity interest held by investigator: 0<br>Sponsor of covered study: LEO Pharma | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes ☐ | No ☐ (Request details from Applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes ☐ | No ☐ (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0 | | |
| Is an attachment provided with the reason: | Yes ☐ | No ☐ (Request explanation from Applicant) |

# 24. References

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# 25. Review Team

**Table 96. Reviewers of Integrated Assessment**

| Role | Name(s) |
|---|---|
| **Regulatory Project Manager** | Strother D. Dixon; Barbara Gould (CPMS) |
| **Nonclinical Reviewer** | Renqin Duan, PhD |
| **Nonclinical Team Leader** | Barbara Hill, PhD |
| **Office of Clinical Pharmacology and Pharmacometrics Reviewer** | Da Zhang, PhD |
| **Office of Clinical Pharmacology Team Leader** | Chinmay Shukla, PhD |
| **Office of Clinical Pharmacology - Pharmacometrics Team Leader** | Jiang Liu, PhD |
| **Clinical Reviewer** | Hamid Tabatabai, MD |
| **Clinical Team Leader** | David Kettl, MD, FAAP |
| **Associate Director for Labeling (Acting)** | Matthew White |
| **Statistical Reviewer** | Marilena Flouri, PhD |
| **Statistical Team Leader** | Mohamed Alosh, PhD |
| **Cross-Disciplinary Team Leader** | David Kettl, MD, FAAP |
| **Division Director (pharm/tox)** | Andrew Goodwin, PhD |
| **Division Director (OCP)** | Suresh Doddapaneni, PhD |
| **Division Director (OB)** | Mahboob Sobhan, PhD |
| **Division Director (clinical)** | Shari Targum MD, MPH, FACP, FACC |
| **Office Director (or designated signatory authority)** | Julie G. Beitz, MD |

OCP, Office of Clinical Pharmacology
OB, Office of Biostatistics

**Table 97. Additional Reviewers of Application**

| Office or Discipline | Name(s) |
|---|---|
| **OPQ** | Yanming An, PhD<br>Samuel Mindaye, PhD<br>Vicky Borders-Hemphill, PhD<br>Xianghong (Emily) Jing, PhD<br>Bruce Huang, PhD<br>Viviana Matta, PhD<br>Candace Gomez-Broughton, PhD<br>Kelly Ballard, MS |
| **Microbiology** | Yarery C. Smith, PhD<br>Zhao (Joe) Wang, PhD |
| **OPDP** | Laurie Buonaccorsi<br>Matthew Falter |
| **PLT** | Shawna Hutchins<br>Barbara Fuller |
| **OSI** | Christian Shenouda, MD<br>Phillip Kronstein, MD |
| **OSE/DEPI** | Catherine Lerro |
| **OSE/DPV** | Vicky Chan<br>Jonn Bailey |
| **OSE/DMEPA** | Madhuri R. Patel, PharmD<br>Ebony Whaley, PharmD, BCPPS |
| **OSE/DRISK** | Carlisha Gentles<br>Yasmeen Abou-Sayed<br>Jacqueline Sheppard |
| **CDRH** | Stephen Retta<br>Rumi Young |
| **DPMH** | Jean Limpert, MD<br>Miriam Dinatale, DO<br>Lynne P. Yao, MD |
| **Other** | Tri Bui Nguyen, PhD |

OPQ, Office of Pharmaceutical Quality
OPDP, Office of Prescription Drug Promotion
OSI, Office of Scientific Investigations
OSE, Office of Surveillance and Epidemiology
DEPI, Division of Epidemiology
DMEPA, Division of Medication Error Prevention and Analysis
DRISK, Division of Risk Management
PLT, Patient Labeling Team
DPV, Division of Pharmacovigilance
DPMH, Division of Pediatric and Maternal Health

**Table 98. Signatures of Reviewers**

| Discipline and Title or Role | Reviewer Name | Office/Division | Sections Authored/ Acknowledged/ Approved |
|---|---|---|---|
| Product Quality | Yanming An, PhD | OPQ/OBP/DBRRII | 9<br>☒ Authored<br>☒ Approved |
| Secondary Reviewer | **Signature:** Yanming An -S Digitally signed by Yanming An -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yanming An -S, 0.9.2342.19200300.100.1.1=2000346981 Date: 2021.04.22 11:38:15 -04'00' | | |
| Pharmacology/Toxicology | Renqin Duan, PhD | OND/OII/DPT-II | 5.2.1, 5.2.2, 7.1, 8.3, 8.4.1, 13<br>☒ Authored<br>☐ Approved |
| Reviewer | **Signature:** Renqin Duan -S Digitally signed by Renqin Duan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Renqin Duan -S, 0.9.2342.19200300.100.1.1=2000362306 Date: 2021.04.22 12:44:06 -04'00' | | |
| Pharmacology/Toxicology | Barbara Hill, PhD | OND/OII/DPT-II | 5.2.1, 5.2.2, 7.1, 8.3, 8.4.1, 13<br>☐ Authored<br>☒ Approved |
| Supervisor | **Signature:** Barbara A. Hill -S Digitally signed by Barbara A. Hill -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300098991, cn=Barbara A. Hill -S Date: 2021.04.22 13:02:29 -04'00' | | |
| Pharmacology/Toxicology | Andrew Goodwin, PhD | OND/OII/DPT-II | 5.2.1,5.2.2, 7.1, 8.3, 8.4.1, 13<br>☐ Authored<br>☒ Approved |
| Division Director | **Signature:** Andrew C. Goodwin -S Digitally signed by Andrew C. Goodwin -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001026825, cn=Andrew C. Goodwin -S Date: 2021.04.22 15:36:48 -04'00' | | |
| Clinical Pharmacology | Da Zhang, PhD | OCP/DIIP | 5 and 14<br>☒ Authored<br>☐ Approved |
| Reviewer | **Signature:** Da Zhang -S Digitally signed by Da Zhang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Da Zhang -S, 0.9.2342.19200300.100.1.1=2012242580 Date: 2021.04.22 14:37:51 -04'00' | | |
| Clinical Pharmacology | Chinmay Shukla, PhD | OCP/DIIP | 5 and 14<br>☐ Authored<br>☒ Approved |
| Team Leader | **Signature:** Chinmay Shukla -S Digitally signed by Chinmay Shukla -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Chinmay Shukla -S, 0.9.2342.19200300.100.1.1=2000377244 Date: 2021.04.22 13:59:09 -04'00' | | |
| Clinical Pharmacology/Pharmacometrics | Jiang Liu, PhD | / OCP/DPM | 5 and 14<br>☐ Authored<br>☒ Approved |
| Team Leader | **Signature:** Jiang Liu -S Digitally signed by Jiang Liu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jiang Liu -S, 0.9.2342.19200300.100.1.1=2000348510 Date: 2021.04.22 14:28:52 -04'00' | | |
| Clinical Pharmacology | Suresh Doddapaneni, PhD | OCP/DIIP | 5 and 14<br>☐ Authored<br>☒ Approved |

| Discipline and Title or Role | Reviewer Name | Office/Division | Sections Authored/ Acknowledged/ Approved |
|---|---|---|---|
| Supervisor | Signature: Suresh N. Doddapaneni -S Digitally signed by Suresh N Doddapaneni S DN: c=US o=U S Government ou=HHS ou=FDA ou=People 0.9.2342.19200300.100.1.1=1300101327 cn=Suresh N Doddapaneni S Date: 2021.04.22 17:08:51 -04'00' | | |
| Biometrics | Marilena Flouri, PhD | OB/DB III | 6.2, III.15, III.16<br>☒ Authored<br>☐ Approved |
| Reviewer | **Signature:** Marilena Flouri -S Digitally signed by Marilena Flouri -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002168509, cn=Marilena Flouri -S Date: 2021.04.22 15:32:47 -04'00' | | |
| Biometrics | Mohamed Alosh, PhD | OB/DB III | 6.2, III.15, III.16<br>☐ Authored<br>☒ Approved |
| Team Leader | **Signature:** Mohamed A. Alosh -S Digitally signed by Mohamed A. Alosh -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300089441, cn=Mohamed A. Alosh -S Date: 2021.04.22 16:19:27 -04'00' | | |
| Biometrics | Mahboob Sobhan, PhD | OB/DB III | 6.2, III.15, III.16<br>☐ Authored<br>☒ Approved |
| Associate Director | **Signature:** Mahboob Sobhan -S Digitally signed by Mahboob Sobhan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mahboob Sobhan -S, 0.9.2342.19200300.100.1.1=1300084769 Date: 2021.04.22 16:15:33 -04'00' | | |
| Clinical | Hamid Tabatabai, MD | OND/ODE3/OII/DDD | First part of 2.1, 3(introduction), 3.2, 4, 7.4, 7.5, 7.6, 10, 11, 12, 17, 20, 23.<br>☒ Authored<br>☐ Approved |
| Reviewer | **Signature:** Hamid Tabatabai -S Digitally signed by Hamid Tabatabai -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002014737, cn=Hamid Tabatabai -S Date: 2021.04.22 17:30:50 -04'00' | | |
| Clinical | David Kettl, MD, FAAP | OND/ODE3/OII/DDD | All<br>☐ Authored<br>☒ Approved |
| Cross-Disciplinary Team Lead | **Signature:** David L. Kettl -S Digitally signed by David L. Kettl -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=David L. Kettl -S, 0.9.2342.19200300.100.1.1=1300383857 Date: 2021.04.22 10:35:18 -04'00' | | |
| Deputy Director | Shari L. Targum, MD, MPH, FACP, FACC | OND/ODE3/OII/DDD | 1 (Authored) & All (Approved)<br>☒ Authored<br>☒ Approved |
| | **Signature:** Shari L. Targum -S Digitally signed by Shari L. Targum -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300149525, cn=Shari L. Targum -S Date: 2021.04.23 11:08:37 -04'00' | | |
| Signatory Authority | Julie G. Beitz, MD | OND/ODE3/OII | All<br>☐ Authored<br>☒ Approved |
| | **Signature:** | | |

Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

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/s/

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STROTHER D DIXON
04/23/2021 04:13:53 PM

JULIE G BEITZ
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